

Th. Sect.

THE THERAPEUTIC EFFECT of DIGITALIS

on the VAGUS

as shown

by

ATROPIN RELEASE.

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MD

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The following statement is made by
SIR THOMAS LEWIS:-

" The conclusion that Digitalis" slows the ventricle by producing block in fibrillation is now generally accepted; but the precise manner in which block is induced is still disputed, Mackenzie holding it to be vagal, and Cushny believing it to be due to direct action on the muscle. The discussion turns largely upon the reaction of the digitalised heart to Atropin. This question will be considered rather fully, because very similar considerations are relevant whenever we desire to determine, whether or not, the vagus is responsible for a slow heart action. It is first to be observed that the dose of Atropin usually given in patients as a test i.e. 1/50 gr, is hardly sufficient or actually insufficient to paralyse the vagi completely. Usually such a dose put the vagus almost, but not entirely, out of action; to produce absolute paralysis doses of 1/10 or 1/5 are probably necessary, and preferably, the dose should be intravenous. Such doses cannot always be given with impunity". (XIV)

Ever since Digitalis was introduced into medicine, there has been considerable doubt as to the manner in which it affects the heart. Most writers and Physicians are agreed that it produces a slowing effect, but they are not agreed as to whether the effect is obtained by:-

(1) The action on the Cardio-Inhibitory Centre,

or,

(2) The action on the Cardiac Muscle.

The object of the present paper is to throw some light, if possible, on the debateable points in view of recent clinical observations on the human heart, by means of the electrocardiograph.

THE SLOWING EFFECT OF DIGITALIS.

The slowing effect of Digitalis must at the onset be considered from three points of view:-

- (1) The Cardiac Rhythm.
- (2) The dose required.
- (3) The time of onset of its full therapeutic action.

(1) CARDIAC RHYTHM:-

All observers have for long been agreed that the action of the drug is quite different when the Cardiac Auricles are in a state of fibrillation, from any response obtained when the pacemaker dictates the rhythm.

For the purpose of this enquiry the rhythm of the heart is always that of Auricular Fibrillation, except where otherwise clearly stated. Patients with spontaneous fibrillation have not been used.

(2) THE DOSE:-

The dose may be given in two different ways, (1) in repeated small doses over a period of time, or, (2), by Eggleston's Massive Method.

In the use of repeated small doses over a long period of time the effect can be obtained in about six days, using $3\bar{I}$ per day. (Mackenzie XVI)

(3) ELIMINATION:-

Pardee has estimated that the Digitalis is eliminated at the rate of min.XXII per day. In our experience min. XXX per day maintains the effect. The proof is obtained from the average dose required Clinically, to maintain the pulse rate at about 90.

Eggleston (IX) states that in the use of Digitalis it has only been given a fair trial when it has been administered to the point of production of one or more criteria of minor intoxication, and to obtain the best results the dose should be just short of the toxic dose.

EGGLESTON'S MASSIVE METHOD of ADMINISTRATION (VII)

is calculated from the body weight of the patient, and tincture of Digitalis is given at the rate of 0.1 cc. per lb. body weight. It is given in three portions at six hourly intervals, and when electrocardiograms are taken at two hourly intervals, an opportunity is afforded of determining the time occupied in the action of the drug.

ASSAY on PATIENTS.

The giving of a massive dose to patients serves to demonstrate the variation in the potency of the tincture, as shown by the degree of slowing, and the occurrence of minor toxic phenomena.

Pardee and Canby Robinson (II), are agreed that after the administration of a massive dose of Digitalis, slowing is fully developed in six hours, and that where the dose approaches the toxic dose the ~~Tens~~ wave of the Electrocardiogram in Lead II is also inverted.

In the course of this work two different tinctures were used, and there was reason to believe that one was much more potent than the other.

Pharmacological Assay may be carried out by several methods, those dependent upon perfusion must introduce a serious potential error, in that the Cardiac conditions are so far removed from normal and the Musculature must suffer some grade of malnutrition. Injection methods, on the other hand are likely to give a full effect of the drug on the heart, but the factor of gastro-intestinal absorption is not taken into account, and this has been shown by Eggleston (VII) to determine largely the therapeutic result obtained.

Doses of the tincture determined by a calculation of cc per lb. body weight can only be satisfactory if the potency of the tincture is fully known.

The Assay of the tinctures should be made by mouth, as much depends on the absorption, and this cannot be estimated so accurately by perfusion methods.

Hatcher and Brodie's method of Assay by cat unit is capable of giving some relative strength, but the ultimate appreciation of potency must be corrected by clinical observations.

ATROPIN RELEASE.

It has long been known that Atropin has the power of paralysing the Vagus (Vagal Release), and produces a considerable rise in the pulse speed. The customary dose is 1/50 gr. hypodermically, but it has been pointed out that this dose is inadequate for a full vagal effect. It is probable that 1/5 of a gr. intravenously is required, to be certain of full vagal release.

So large a dose given intravenously to the human subject, under clinical observation, would be difficult to justify. But it has been found that 1/25 gr. given intravenously, although causing some discomforts, such as vertigo, dry mouth, dilatation of the pupils etc., produces no other serious effects, and gives in the majority of cases a satisfactory vagal release, with an onset, in point of time, which can be clearly recognised.

Whether this dose is really sufficient to produce complete vagal release, after Digitalis has been given to the point of definite toxicity is doubtful, and remains to be elucidated in the future.

PREVIOUS EXPERIMENTS.

Enquiry along these lines has been carried out, both in animals and in the human subject, but results obtained have been equivocal.

(1) ON ANIMALS.

Traube (IV). Traube showed in 1851 that Digitalis acted on the Vagus in animals, and slowed the pulse, also that the effect disappeared when the Vagi were cut or paralysed with Atropin.

(2) HIRSCHFELDER. (XII)

Hirschfelder, working with dogs and cats, in which fibrillation had been artificially induced, concluded that Digitalis' effect could be completely obliterated by Atropin, except when complete block (a toxic effect) had been reached.

(3) GREEN BOUTWELL & PEELER. (XI), perfused Digitalis

through the Cardiac muscles of the Terrapin, and showed that Digitalis' effect was upon the central end of the Vagus, and this effect was completely ablated by vagal section. They also showed that it was possible to produce an increase in rhythm, increase in amplitude of contractions, and increase in a state of tonic contractions, by Digitalis on isolated strips of Cardiac muscle after treatment with Atropin.

They concluded that there was evidence for the belief that Digitalis acted by (a) stimulation of the Cardiac inhibitory Centre.

(b) by direct stimulation of the Cardiac Muscle.

(4) CANBY ROBINSON (II) slowly administered a diluted Tincture of Digitalis intravenously into a series of cats, and followed the effects of the drug by electrocardiograms. In these experiments the heart rate was slowed gradually, the effect being first seen with about 25% of the Minimal Lethal Dose, while the maximal slowing occurred when about 70% of the M.L.D had been given.

In a second series of cats, in which the vagi had been cut, practically no slowing of the heart was observed.

(5). CUSHNY (V) in his animal experiments found that when the Auricle was thrown into fibrillation by electrical stimulation the ventricle could be slowed by intravenous injection of Digitalis or Strophanthin, and that the slowing disappeared on section of the vagus or after Atropin, Thus showing that the effect was purely due to excessive activity of the inhibitory mechanism, mainly of the medullary centre.

He also showed that when inhibition was eliminated by previous section of the vagus, or by Atropin, the fatal action of Digitalis and its allies was delayed, and that the Minimal Lethal Dose was higher than in uninjured animals.

He believes that Atropin given after Digitalis does not quicken the heart as much as when given before Digitalis, and in order to prove it, did many animal experiments

with perfused hearts.

He decided there were two types of hearts acted on by Digitalis.

- (a) Those on which a purely inhibitory effect was obtained through central vagal stimulation,
- (b) Those in which the action of Digitalis was directly on the conducting tissues, and unaffected by Atropin, and found typically in malnourished hearts - believing it to be common in Auricular Fibrillation.

(6) TABORA (XIX) found that after mechanical injury to the fibres of ~~His~~ the conduction was very readily paralysed by Digitalis.

(7) BRAUN & MAGER (I) found that by perfusing animals' hearts with Digitalis they got a transient increase in rate followed by slowing, which they differentiate into two forms -

- (a) One removed by Atropin, and therefore inhibitory in character

- (b) One unaffected by Atropin.

These experiments were of only short duration, seldom lasting more than ten minutes, and often less than five minutes after the administration of Digitalis, and their statement that Atropin removes one form of slowing was therefore not considered by Cushny to be founded on satisfactory grounds.

Owing to an error in numbering

pages 10 & 11 were

omitted.

CRITICISM OF ANIMAL EXPERIMENTS.

It must not be forgotten that in Animal experiments the circumstances under which the results are obtained, are not always pertaining to the normal course of the heart's action. Cushny admits that the perfused heart has been shown to be altered in its reaction to various procedures. i.e. the plasma of its own blood may ^{BE} _^injurious to it, and its reaction to electrical stimulation is changed.

On the other hand one has the opportunity of experimenting with much larger doses of drugs than one could safely try on the human subject.

The results of the experiments with Digitalis and Atropin in animals serves to show that in the majority of cases Digitalis acts on the vagus rather than on the Cardiac Muscle, and gives complete release after Atropin.

Deductions applicable to man, cannot be made from animal experiments, in which doses of the drug have been used either,

- (a) in excess of the toxic dose, or,
- (b) by abnormal routes i.e. the intravenous one, or the perfusion method.

II. ON HUMAN BEINGS.

A good many experiments on Atropin Release have been tried on animals, but very few on human beings .

(1) CUSHNEY, MARRIS & SILBERBERG (III) experimented with a series of non-fibrillating hearts, and with a series of fibrillating ones.

In the series of five cases of non-fibrillating hearts, the cases were treated for 5-7 days with Tincture Digitalis m.XX, thrice daily, and then released with Atropin 1/50- 1/25 gr. given subcutaneously, and the heart rate was counted by polygraph every five minutes afterwards.

In the first three cases the injection of Atropin was followed by the disappearance of the slowing and irregularity induced by Digitalis, and these were accordingly ascribed to the inhibitory action.

In cases four and five, where the stage of block was reached, these were unaffected by atropin and were therefore considered as cases where Digitalis had acted on the muscle.

In the ten cases of fibrillation, the cases were given Tinct.Digitalis m.XX. thrice daily from 5-7 days, and then released by 1/50 gr. of Atropin, subcutaneously, and the rate was counted by polygraph every five minutes.

The following is a table of the results obtained,

	Rate without Digitalis..	Rate after Atropin.	Rate under Digitalis.	Atropin after Digitalis..
1.	90-100.	134-144	60-64	76-84
2.	76- 86	130-140	66-72	74-86
3.	120-130	180-190	70	90-96
4.	110-130	170-176	76-78	86-92
5.	70-80	90-100	58-60	84-92
6.	118-122	120-132	64-74	68-74
7.	106-110	124	52	55-59
8.	104-112	148-159	64-69	74-84
9.	83-87	130-140	57	76
10.	120	160	71-79	74-81.

They summarise their results as follows:-

1. The members of the Digitalis group slow the pulse in a certain number of cases in which the rhythm is given by the normal pace maker, and as a general rule, the slowing may be removed by Atropin, and is therefore inhibitory. In other cases however, the sinus slowing and block are unchanged by Atropin, and they arise from the direct action of the Digitalis on the conducting fibres from the pace maker to the Auricle, and from Auricle to Ventricle.

2. In Auricular Fibrillation, Digitalis, and its allies slow the heart from some direct action on the heart, and not from stimulation, of the inhibitory mechanism, for atropin does not restore the original rate of the released heart. The reduction in rate may be due to a direct depression of the conduction or of the excitability of the heart muscle by Digitalis. But it is suggested that these functions are reduced indirectly through the improved nutrition of the heart from the augmented power of contraction of the heart muscle.

3. The inhibitory stimulation induced by Digitalis does not play any part in the beneficial action of the drug, which is ascribed to its direct action on the cardiac muscle only..

CRITICISM OF METHOD OF CUSHNY, MARRIS & SILBERBERG.

The criticism offered on the foregoing experiments is as follows:-

- (1). The dose of Atropin was too small, and therefore, the full effect was probably not obtained.
- (2) The Atropin was injected subcutaneously, and therefore, the reaction was not very reliable in amount or in time.
- (3) From the intermittent periods of time in counting the maximum time of release could not be gauged accurately.

2. EMANUEL (X) discusses the effect of Digitalis on the vagus and considers that Digitalis acts on both the Vagi and the Cardiac muscle, the earlier effect being vagal, and later the bundle itself being directly affected.

He quotes the following case:-

A.B. age 60, was suffering from Cardiac failure with oedema, the result of Auricular Fibrillation.

Emanuel gave him a series of injections of Atropin, before and after a very large dose of Digitalis

The chart appended covers a period of 37 days, showing the slowing effect of Digitalis, and the accelerating effect of Atropin, 9 granules of Nativelles Digitalin (gns. 1/240) were given on 3rd. April in the course of

24 hours.

Atropin Sulphate gns $1/30$ was given subcutaneously, on the days indicated. On April 2nd before the digitalis was given, the Atropin produced an acceleration of 54 Ventricular beats (126-180). On the 4th April the same dose of Atropin caused an approximately equal acceleration of 46 beats (90-136), although the heart was under the influence of Digitalis as shown by the slowing from 126-90. The Atropin on the 6th and the 8th of April only produced an acceleration of 15 beats (85-100) and 10 beats (82-92) respectively, the suggestion being that on the 4th April the effect of the Digitalis was entirely Vagal, and capable therefore of being abolished by Atropin, whereas, by April 6th, the Digitalis had affected the Cardiac muscle as well, and therefore, the Atropin was comparatively ineffectual. After the fourth injection, the effect of Digitalis began to pass off and the Atropin was again able to exert unrestricted action.

The following were his results obtained:-

<u>Date.</u>	<u>Increase in rate after 1/30 gr. Atropin.</u>
April 2nd.	126 - 180 beats per minute.
4th.	90 - 136 " " "
6th.	85 - 100 " " "
8th	82 - 92 " " "
13th.	75 - 115 " " "
15th	70 - 102 " " "
17th	75 - 120 " " "
20th.	80 - 102 " " "
23rd.	75 - 115 " " "
27th.	80 - 115 " " "
May 2nd.	85 - 135 " " "

The same criticisms of the experiment can also be offered as upon those of Cushny, Marris & Silberberg, with the additional one on the smallness of the number of cases on which to base a conclusion.

3. WEDD. (XX) Wedd studied the effects of Atropin after full doses of Digitalis in a series of patients.

In thirteen examples of Auricular Fibrillation the patients were given 10 cc. Tint. Digitalis daily till full toxic effects were produced. Atropin 1/33 gr (2 mgs) was injected before and after digitalisation, and the release obtained was far from complete, the difference being variable in two cases, amounting to 60 beats, and 72 beats.

In thirteen cases of normal rhythm the release was incomplete by 4 - 32 beats, and in others there was an increase in escape after Digitalis by 3 - 4- 17 beats. Three cases showed no release whatever.

Wedd concluded that in all cases the action of Digitalis is both central in the Medulla, and local in the myocardium. He observed that in 100% of his cases of Auricular Fibrillation, and in 76% of those with normal rhythm, the heart rate failed to return after Atropin injections to the level at which it was before being slowed by Digitalis. He believes that it is possible therefore, to measure the local action of the drug by the degree which Atropin fails to restore the heart to its original rate.

HALSEY (XIII) Halsey has reported a case showing profound effects brought on apparently by excessive vagus. Stimulation producing severe subjective symptoms, followed the administration of Digitalis to a patient with

Auricular Fibrillation; severe cardiac failure, and Cheyne Stokes breathing. Marked variation in the Ventricular rate from 100-50 beats per minute were observed; the rapid rate occurring during periods of Apnoea. This phenomenon apparently interfered with interchange of O_2 and CO_2 and was relieved by Atropin when the Ventricular rate became 150 per minute.

From which it would appear that in those rare cases of hypersensitivity to Digitalis with the production of early toxic effects, relief can be completely afforded by Atropin. Such effects would therefore appear to be vagal in origin.

5. WHITE AND SATTLER (XXI) White and Sattler found in ten healthy young adults, that Atropin completely removed the effect on the Auricular-Ventricular conduction, and they concluded that the effect on conduction was almost, if not entirely due to increase of vagal tone and irritability, and was identical with the well known results of direct electrical stimulation.

6. RITCHIE (XVIII) quotes a case of removal of Digitalis Coupling by Atropin, where the pulse rate remained the same.

7. COHN & FRANCIS (FRASER (VI)) Cohn and Fraser call attention to the fact that it is useful to distinguish between restoring the rate of the heart (releasing the rate) and restoring the conduction time (releasing the

conduction) to the state in which these were before Digitalis was given. In the numerous times that Atropin was given to the patients a release of the rate occurred in all but one; in about one half of the cases the release was complete i.e. the rate returned to a height as great, or greater, than prevailed before. In other cases where the release was partial the rate rose slightly. But in conduction the release was complete, or all but complete, and a return to normal conditions occurred in all cases, no matter what the degree of intoxication.

This occurred whether Digitalis had produced merely an increase in the length of the conduction time, or an incomplete block, or a complete dissociation. In other words a Sequential ^{1:1} Rhythm was restored. They wish to call attention to the fact that there is a difference between release in rate and release in conduction, and that this difference may occur in the same patient at the same time. In one of the patients who had a normal heart, the rate during extreme intoxication was somewhat depressed, and incomplete block was present. At this time Atropin failed to release the rate, but the conduction time was released practically to normal.

CUSHNY (V)

The actions and uses in Medicine of Digitalis & its Allies 1925.

The vast amount of work and thought devoted by Cushny to this subject makes it difficult to review or to criticise. It is only possible to deal with

some of the more outstanding features in the human experiments,

(1) He concluded that two different effects occur under Digitalis' action.

(A) Inhibitory slowing - occurs in normal Cardiac Rhythm, in man and animals.

(B) Slowing through direct Cardiac action - occurs in most cases of Auricular Fibrillation in man, in rare cases of normal rhythm in man, and in the perfused mammalian heart, either in normal rhythm or fibrillating.

The primary cause of type B response (direct Digitalis action) is the malnutrition of the heart; Auricular Fibrillation merely favours its appearance by accentuating the fundamental cardiac malnutrition.

(2) In no case recorded by him was Atropin given, either intravenously or in Lewis' adequate dose.

(3) Digitalis was normally administered to the toxic stage, vomiting had actually occurred in most cases.

These findings turn upon the presence or absence of full Atropin release after Digitalis; the criticism of dosage and method of administration must of course apply.

To attribute type B. to Cardiac malnutrition is somewhat difficult, in view of the fact that it is well known, and graphic records (VIII p.362. fig.339) exist, to show that the change from fibrillation to normal rhythm under quinidine administration, may and does

occur suddenly at one beat - yet the form of ventricular complex remains quite unchanged, and no graphic evidence can be adduced to show that the heart itself suffered^s in any way from the supposed malnutrition.

Further, the opinion is expressed that the first slowing of Digitalis' action in Auricular Fibrillation is due to ~~both~~ its effect^{both} on the Vagus, and the Auriculo-Ventricular bundle, but that the longer ~~that~~ the action of the drug lasts, the less is the rôle played by the Vagus.

The bearing of this argument on the present work is so considerable, that a special table is provided to show the effect of atropin upon patients who had been under continuous Digitalis' administration for many months, and whose speed had been adequately controlled thereby.

Further a graph is included to show the degree of Atropin release obtained in the same individual. -

- (a) Before Digitalis administration.
- (b) after Digitalis by Massive dose.
- (c) after three months continuous Digitalis administration, during which min. 40 per day of the Tincture was taken.

Two experimnts on the human subject are quoted by Cushny . In both cases the effect of Atropin was tried before and after digitalisation of the heart. In the first experiemnt the pulse rate was 85, and after the injection of 1/50 gr. of Atropin (presumably hypodermically) the

rate rose to 135. Digitalis treatment was then instituted (dose not given) for 10 days and the pulse rate fell down from 85-60 per minute. During those 10 days three injections of Atropin were given and the rate rose to 105, 85, and 75, increasing on two subsequent occasions 25-50 days later to 85, 95, & 140, as the effect of Digitalis began to wear off.

In the second experiment the pulse rate before treatment was 90-102, and was accelerated by 1/50 grs. of Atropin hypodermically to about 140. After treatment for some days with Digitalis (dose not given) the pulse was reduced to 60 -65 and the same injection of Atropin accelerated it only to about 85.

In reviewing the human cases recorded, one is struck by the low speed of the heart after Digitalis administration, speeds of 60 and thereabouts are frequently recorded. Such speeds are usually associated with marked toxic effects, and as pointed out elsewhere in this paper (page (5) it still appears justifiable to believe that a dose of Atropin with proportional toxic effects may be necessary to give a full release. Such experiments still seem unjustified in Clinical work, for should severe Atropin effects occur, it is by no means certain what dose of pilocarpine would be required to counteract the Atropin, nor that the two drugs are so completely antagonistic as to relieve the patient completely.

The fact that incomplete Atropin release has been obtained in the course of this work in two cases which

showed early toxic signs (vomiting) rather supports the view that the patients treated with Digitalis by Cushny, were reduced to a considerable grade of Digitalis "Toxaemia". In fact to such a grade as would be regarded by the Clinician as a Therapeutic error, ^{to} ~~and~~ be avoided.

The two cases recorded in this work, received tincture of Digitalis at the rate of 0.15 cc and 0.175cc per lb. body weight respectively. The former vomited four times after the drug, the latter frequently, and developed a cerebral embolus, with subsequent hemiplegia which recovered later.

The Ventricular speeds in both cases were as follows:-

Case No.	Digitalis Dose.	<u>BEFORE DIGITALIS.</u>		<u>AFTER DIGITALIS</u>	
		Before Atropin.	After Atropin.	Before Atropin.	After Atropin.
21.	0.15	168	204.	96.	120
32.	0.175	144	204	96.	132.

In further criticism of all these experiments, it is pointed out, firstly, that the method of action of Digitalis in this series of experiments requires several days to take full effect, and this prolongs the experiment. It allows other changes to take place in the patient, i.e. several days of rest in bed will change the nutritional and rest conditions of the heart.

Secondly, the administration^{of} atropin was hypodermic presumably, as no statement to the contrary is made. The dose is known to be too small to paralyse the Vagus, and the moment of maximum activity is not known, and is sure to vary with the period of absorption, a recognised variable factor in all hypodermic treatments.

Thirdly, where the pulse rate was counted by non-graphic methods, which are notoriously inaccurate in the presence of gross irregularity and high speed, the exact moment of release by atropin may have been missed.

ATROPIN RELEASE.

The cases were divided into three groups:-

- (1) Digitalis was given to non-fibrillating cases and they were released.
- (2) Digitalis was given to fibrillating cases who had been Digitalis free for one month, and released.
- (3) Cases of fibrillation which had been kept at a reasonable pulse speed under prolonged, and continuous digitalis administration were released.

METHOD USED.

- (1) The patients had had no Digitalis for one month, (except group 3)
- (2) The dose of Digitalis was calculated per lb. body weight.
- (3) The whole experiment was complete in 8 hours.
- (4) Continuous electrocardiographic tracings were taken over the times of observation of Atropin effect. i.e. 2 minutes.
- (5) Atropin 1/25 gr. was given intravenously.
- (1) It was essential to know that the patient was Digitalis free. One month gives freedom, though the actual time is probably 10 days, as observed clinically when patients are deprived of the drug.
- (2) The dose of Digitalis used was calculated at 0.1 cc per lb. body weight of the patient - lately with standard 100% Tinct. Digitalis from the Pharmacological Society's Laboratories, the dose was raised from 0.1cc to 0.125 cc

and in some cases to 0.15 cc per lb body weight.

(3) ACTUAL EXPERIMENT.

The patient was placed in the Cardiographic Circuit and a few complexes recorded on the paper camera, the hypodermic needle was then inserted into the vein, and the camera started again. Further complexes were recorded, and the atropin injected, and the moment of completed injection marked on the paper. The tracing was then continued for two minutes. The patient was then given a massive dose of Digitalis calculated according to weight. i.e.

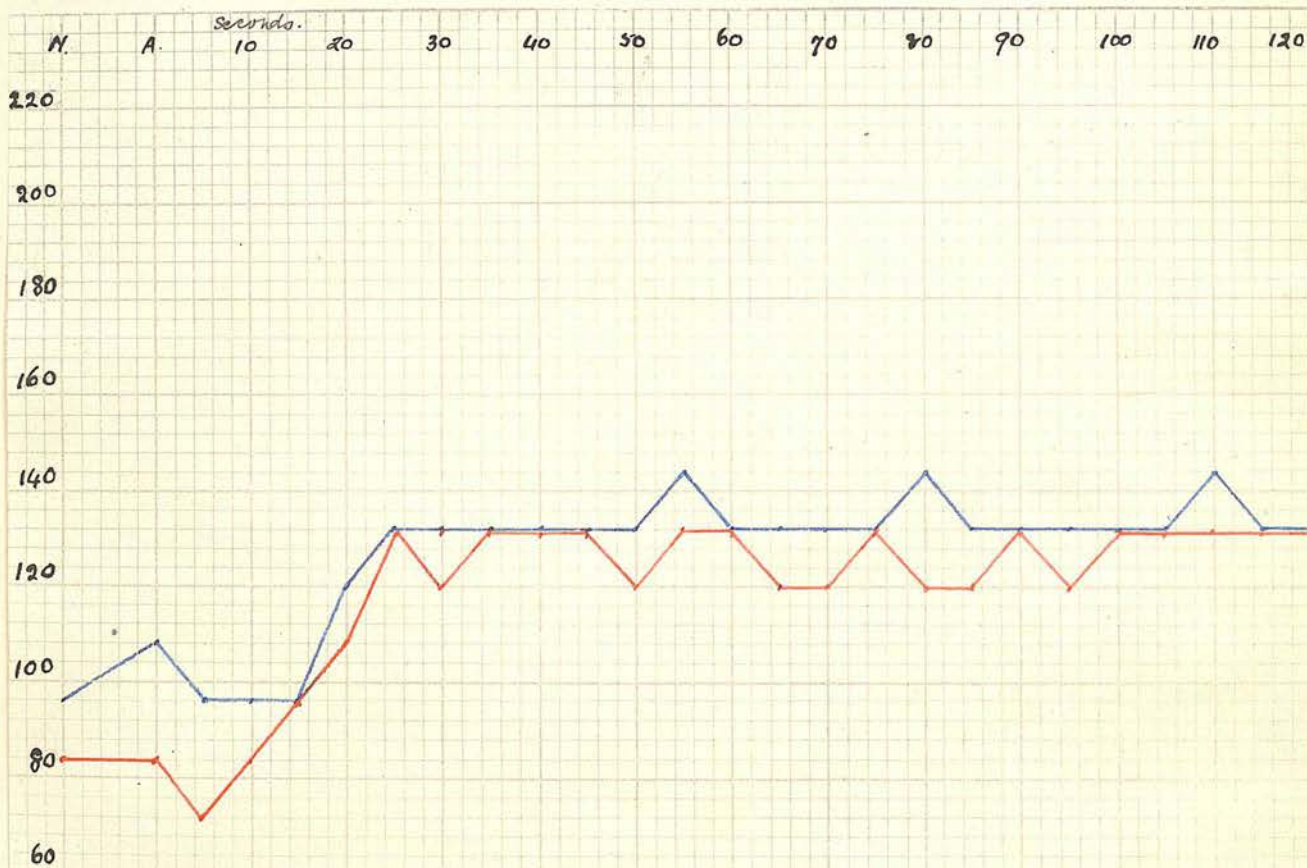
T.Digitalis ccs 15.2 (average dose)
Sod.Bic. gns XV
Sp.Amm.Co. m X.
Aq.Chlorof } III fiat Haust.

The patient then returned to bed for 8 hours, when the tracing experiment and another intravenous injection of 1/25 gr Atropin were repeated.

In analysing the results the paper tracing was counted out in 5 second intervals, and recorded as shown in the following graphs.



NORMAL HEART.



40

Pulse
rate

Name A.T.

age 24.

24.1.27.

Normal Heart.

T. Digit. 13. cc.

Atropin Release.

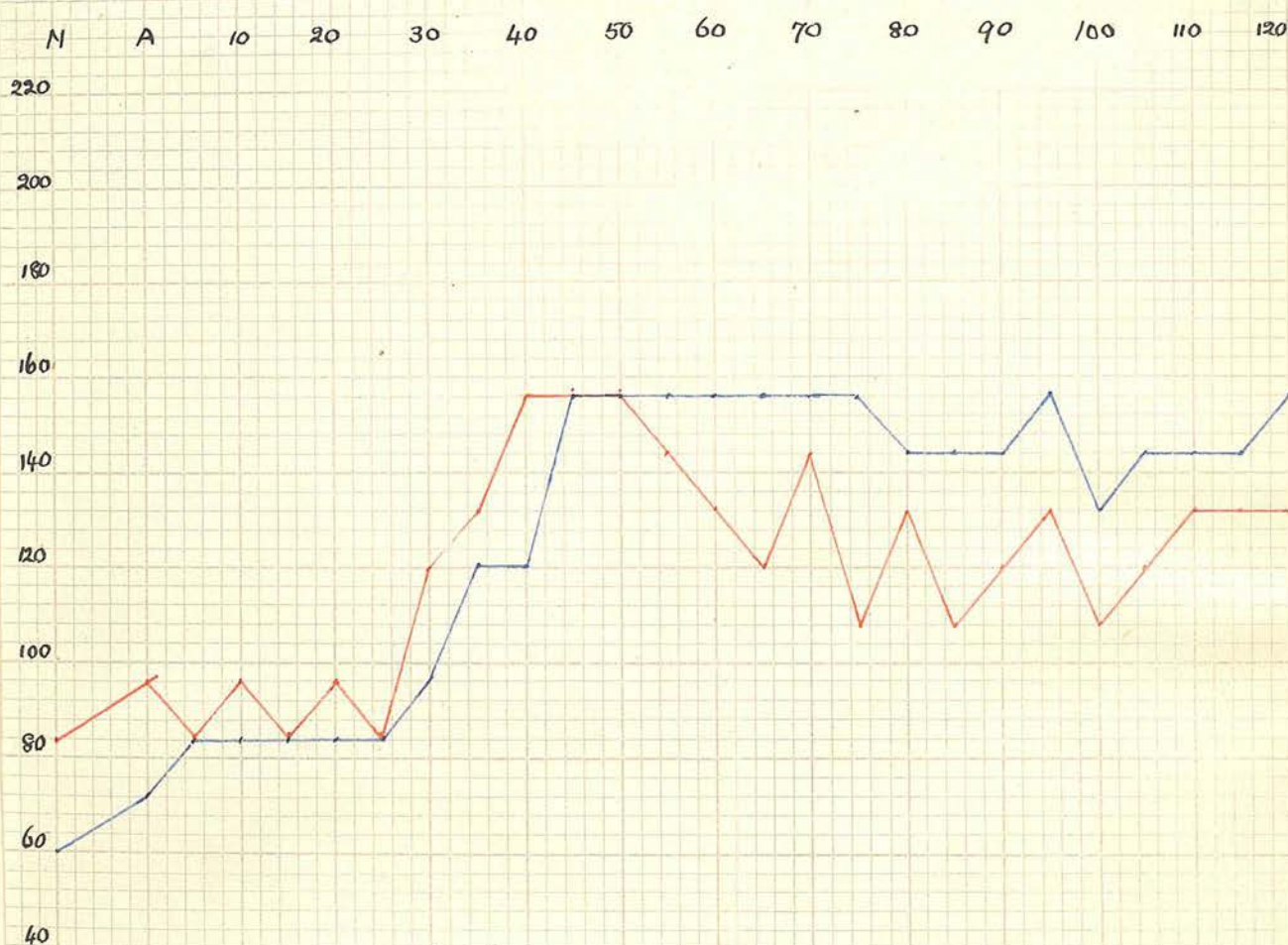
Before Digit - black

after Digit - red

N - before needle

A - atropin injected.

COMPLETE RELEASE.



Pulse
rate

Name. Robt. Ritchie.
age 40.

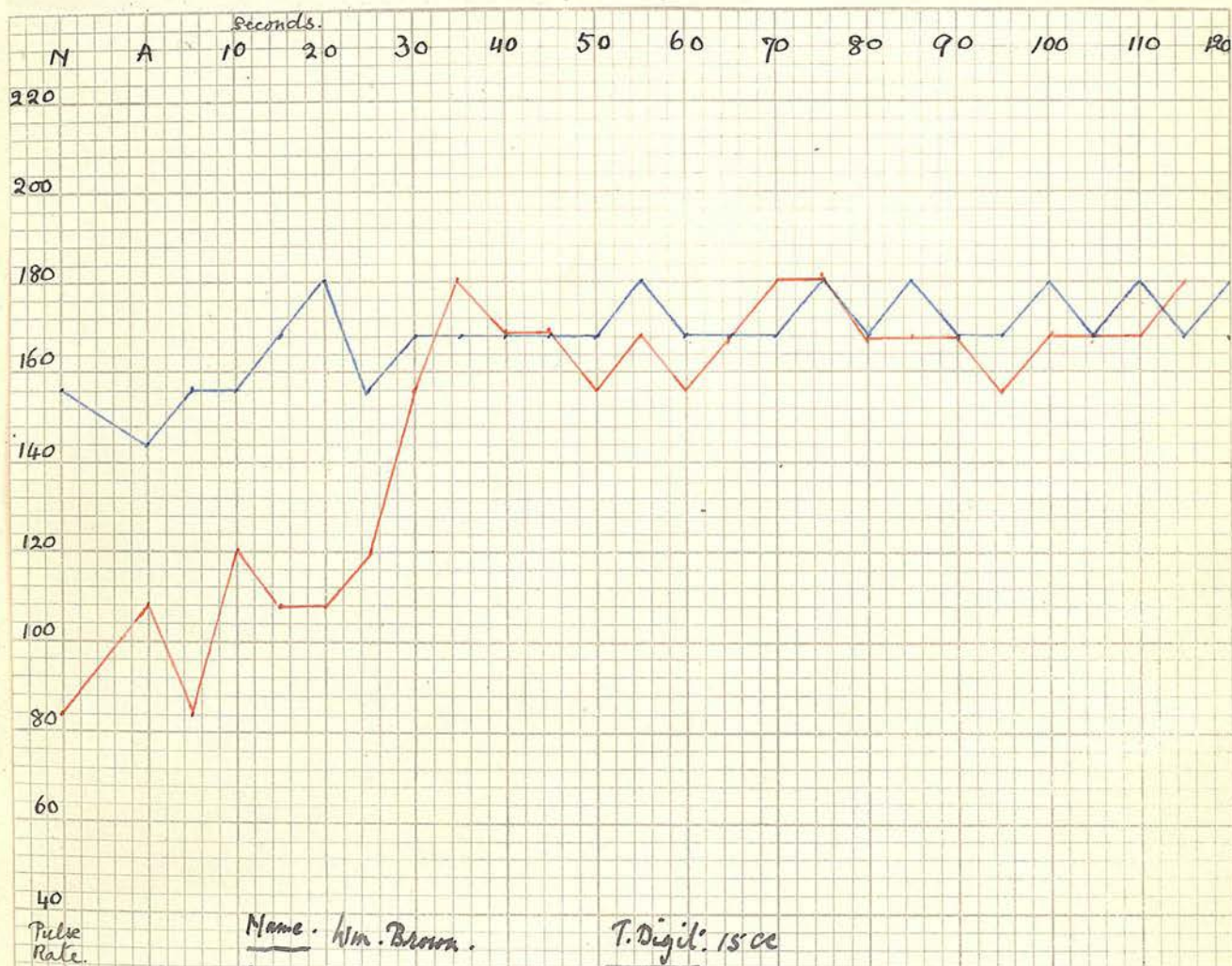
T. Digit. 13.6 cc

Auricular Irrigation
always slow without Dig.

Atropin Release. Bef. Digit - black.
after Digit - red.
N - bef. needle.
A - atropin injected.

COMPLETE

RELEASE.



Name. Wm. Brown.

Age 41.

Quinn's Fibrillation.

T. Digil. 15 cc

Atropin Release

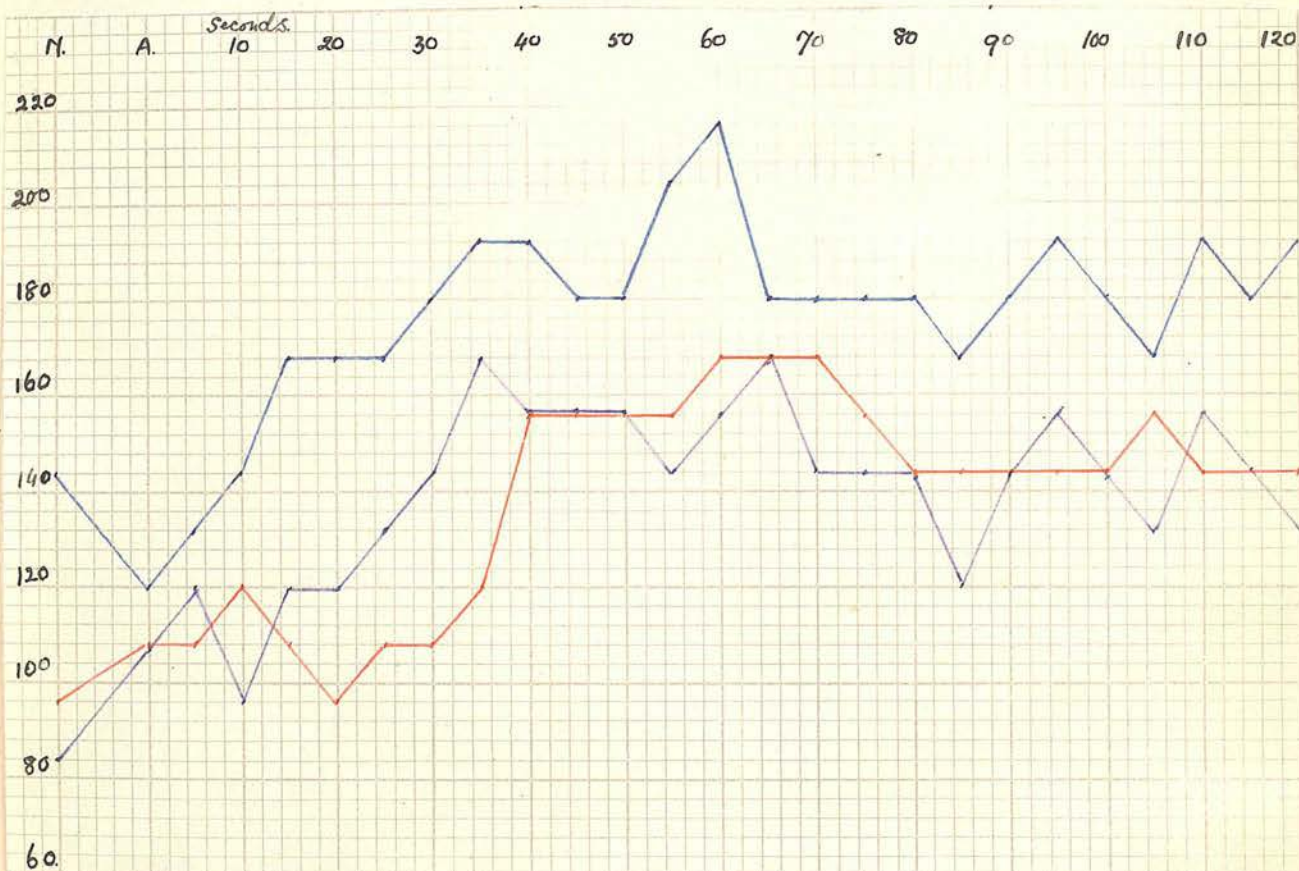
Before Digil. - black

After Digil. - red.

N. - before needle.

A - after injected.

INCOMPLETE RELEASE.



40.

Pulse
rate.

Name. C.B. case 31.

Age 57.

12.1.27.

T. Digit. 15.3 cc

Atropin Release

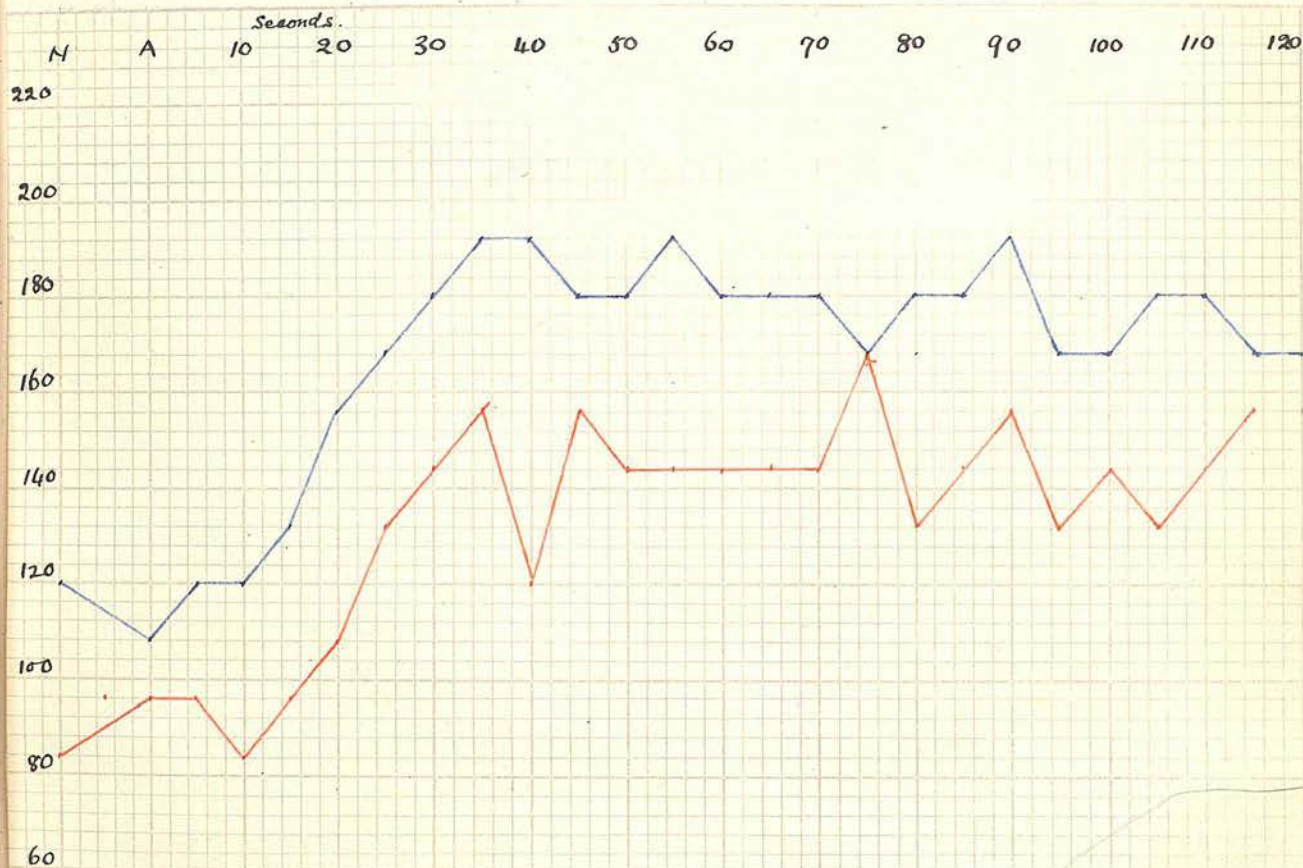
Auricular Fibrillation.

Before Digit. - black
after Digit. - red.
after continued Digit. - mauve.

N - before needle.

A - atropin injected.

INCOMPLETE RELEASE.



140
Pulse
rate.

Name Maxel Morley
age 31.

Antic. Fibrillation

T. Dig it 12.7 cc

Atropin Release

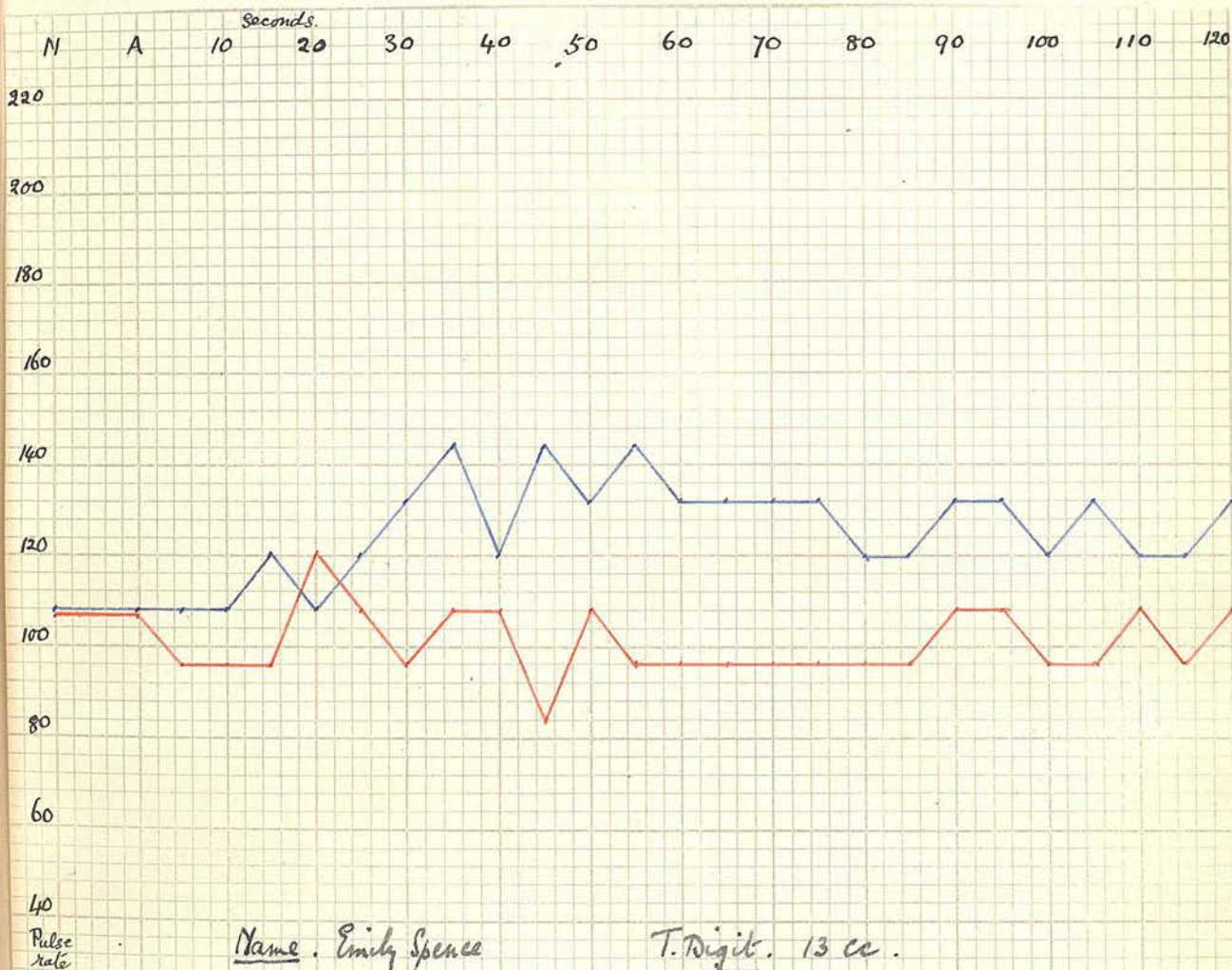
Bef. Dig it - black.

after Dig it - red.

N. - bef. needle.

A - atropin injected.

INCOMPLETE RELEASE.



Name. Emily Spence
age 46

7.1.27.

Arise. Fibrillation

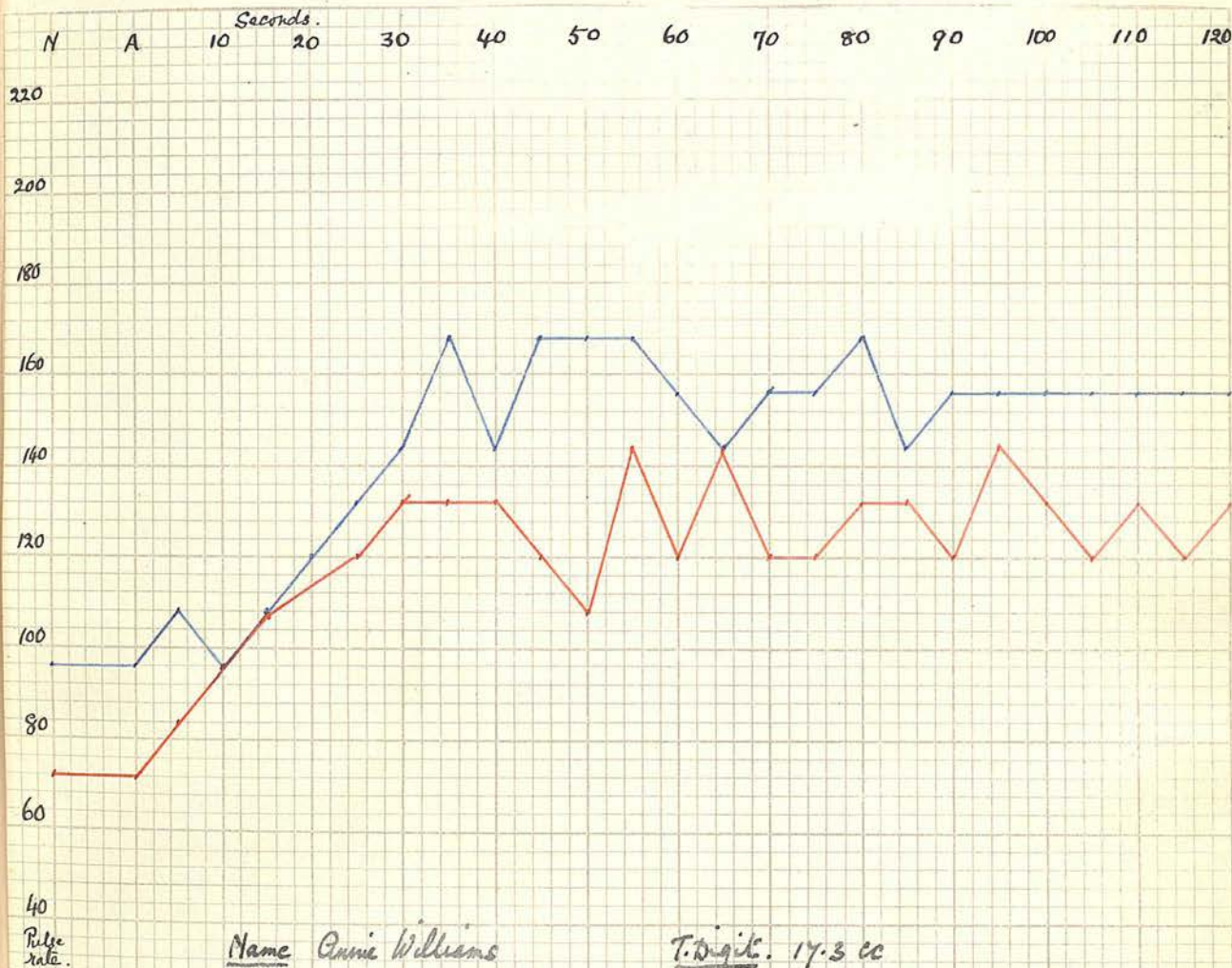
T. Digit. 13 cc.

Atropin Release

Ref. Digit - black.
after Digit - red.

N - hyp. needle.
A - atrop. injected.

INCOMPLETE RELEASE.



Name Annie Williams
age 64.

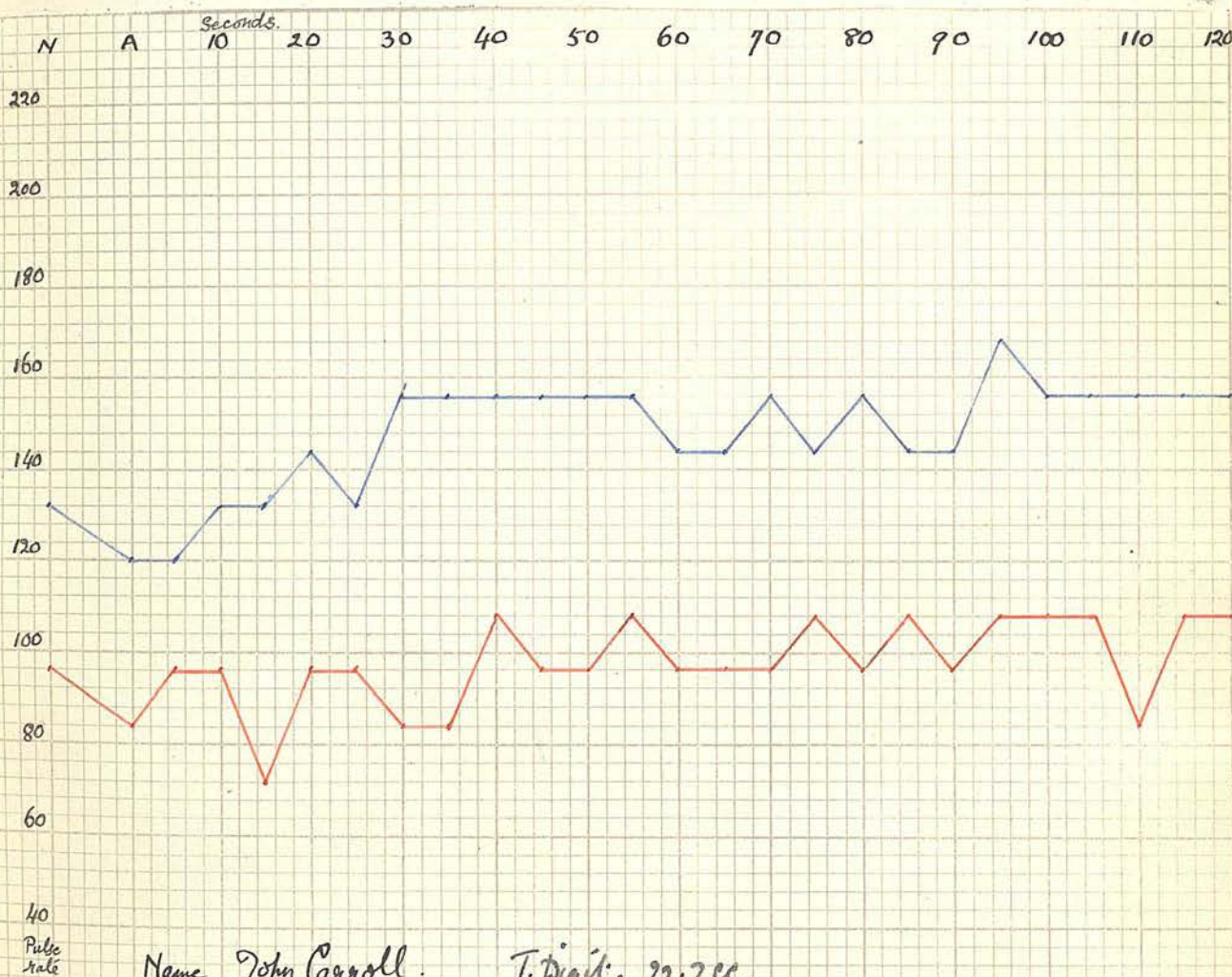
T. Digit. 17.3 cc

Annie. Fibrillation.

Atropin Release Bef. Digit - black.
after Digit - red.

N - bef. needle
A - Atrop. injected.

INCOMPLETE RELEASE.



Name John Carroll.

T. Digit: 22.7 cc.

age 45

Atropin Release

Def. Digit: - black.

3.2.27

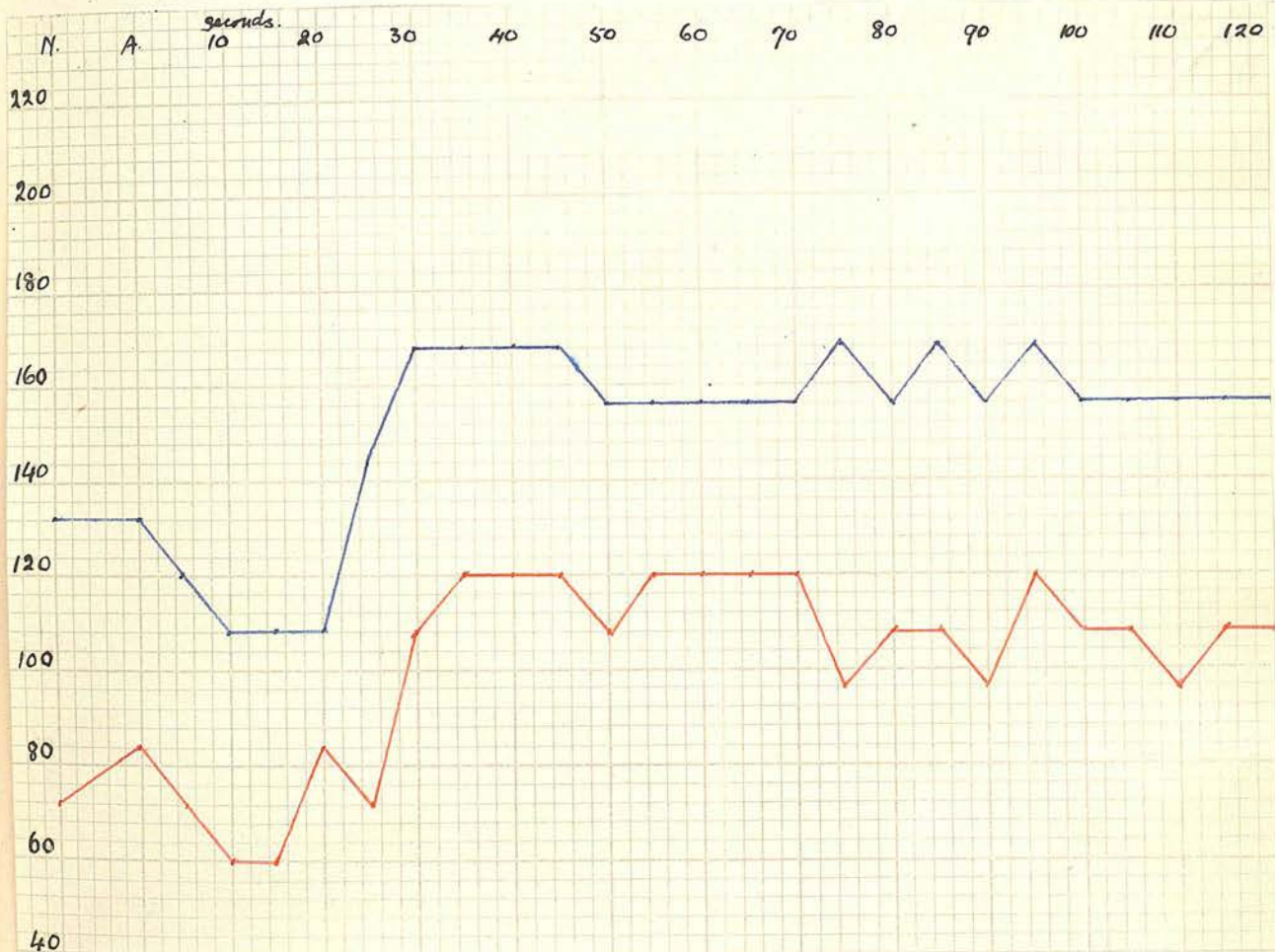
after Digit: - red.

Arris. Fibrillation.

M - before needle.

A - atrop. injected.

INCOMPLETE RELEASE.



40
pulse
rate.

Name. S.B.

age. 39.

21. 1. 27.

Arricular Fibrillation.

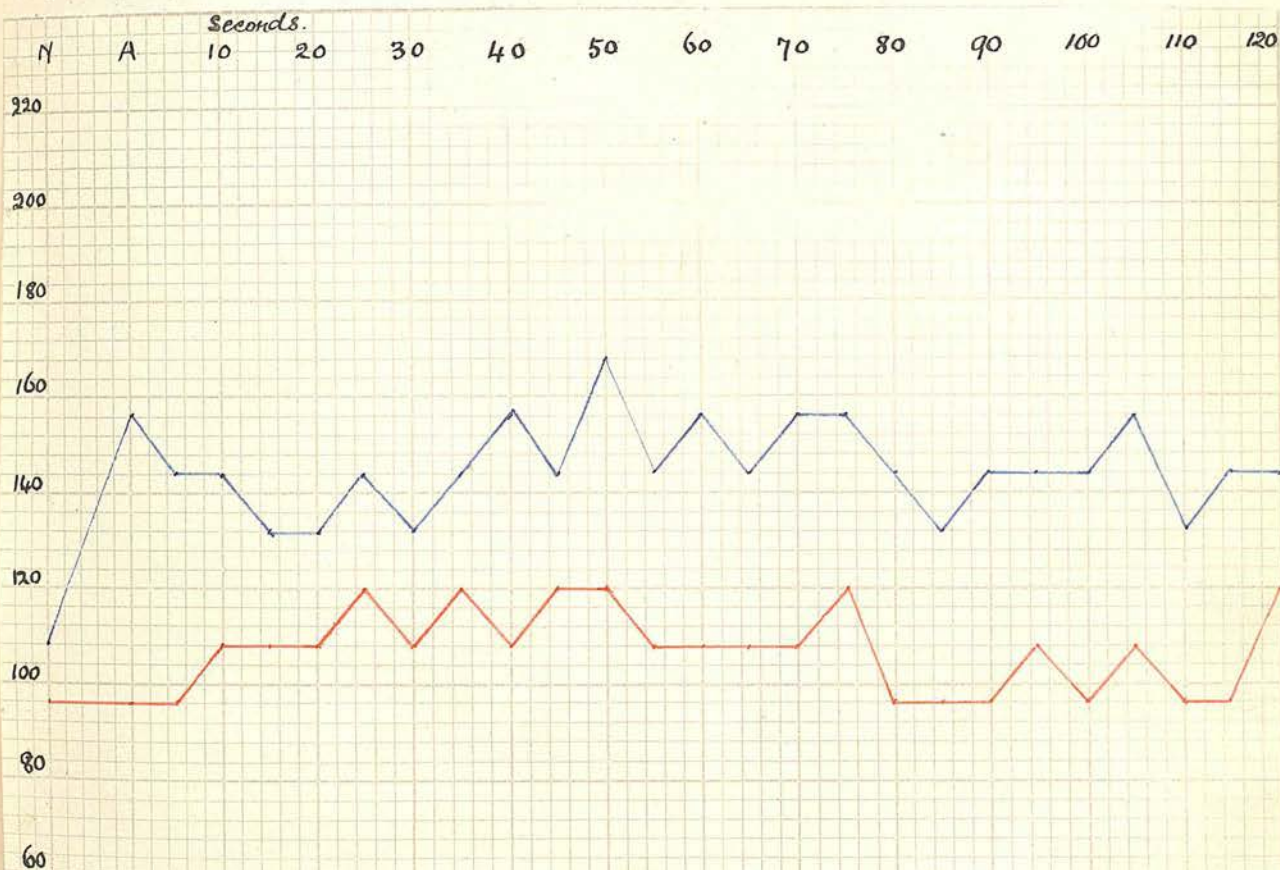
T. Digit. 18.5 cc.

Atropin Release. Before Digit - black
after Digit - red.

N - before needle

A - atropin injected.

INCOMPLETE RELEASE.



Pulse
rate.

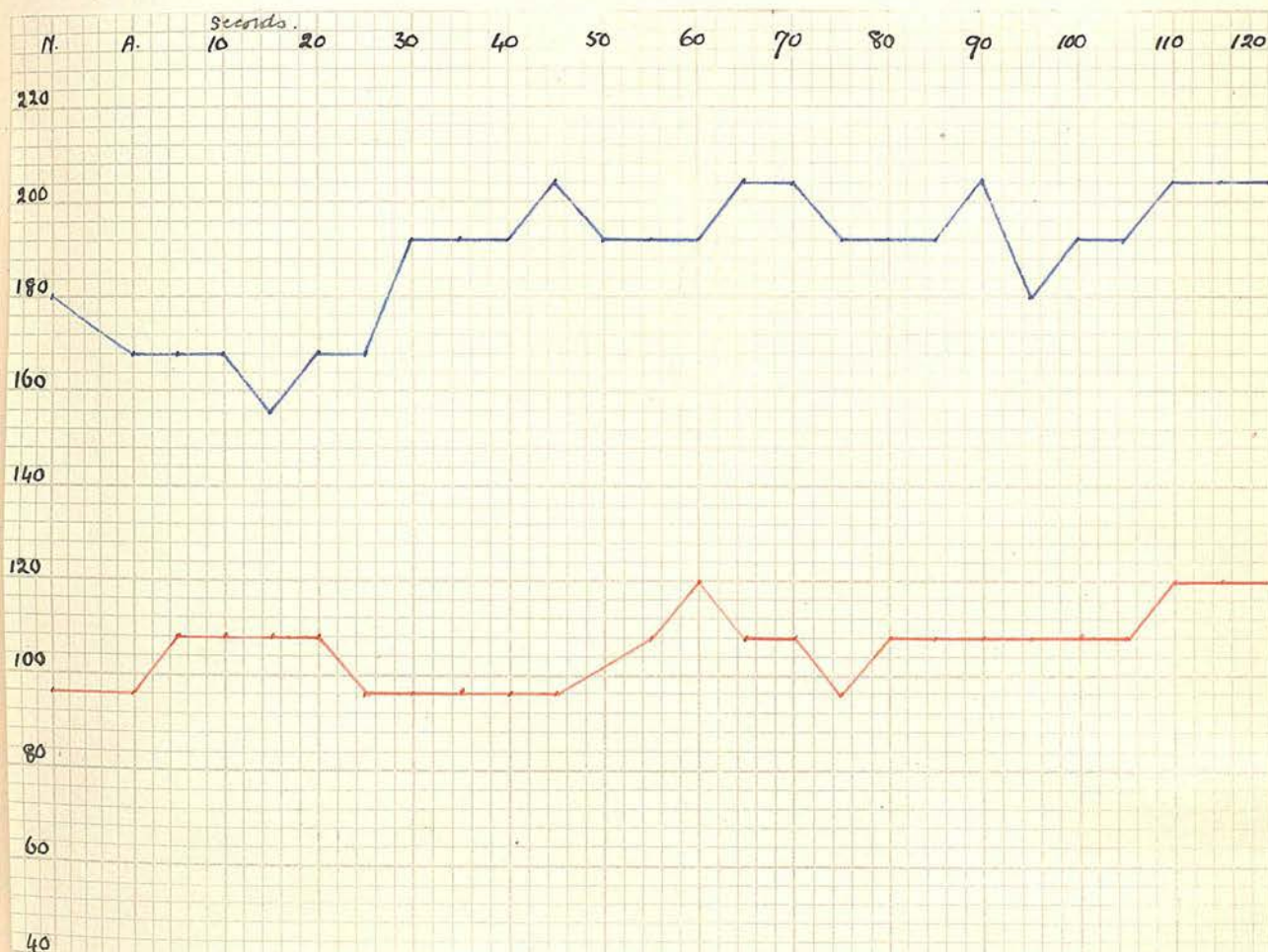
Name. Eliza Macdonald
age 47.

Quinn. Filtration

T. Digit. 11.3 cc.

Atropin Release. Bef. Digit. - black.
after Digit. - red.
N. - bef. needle
A. - Atropin injected

NO RELEASE.



Pulse rate

Name E.C.

age .36.

14.2.27.

Auricular Fibrillation.

T. Digit. 36.5 cc

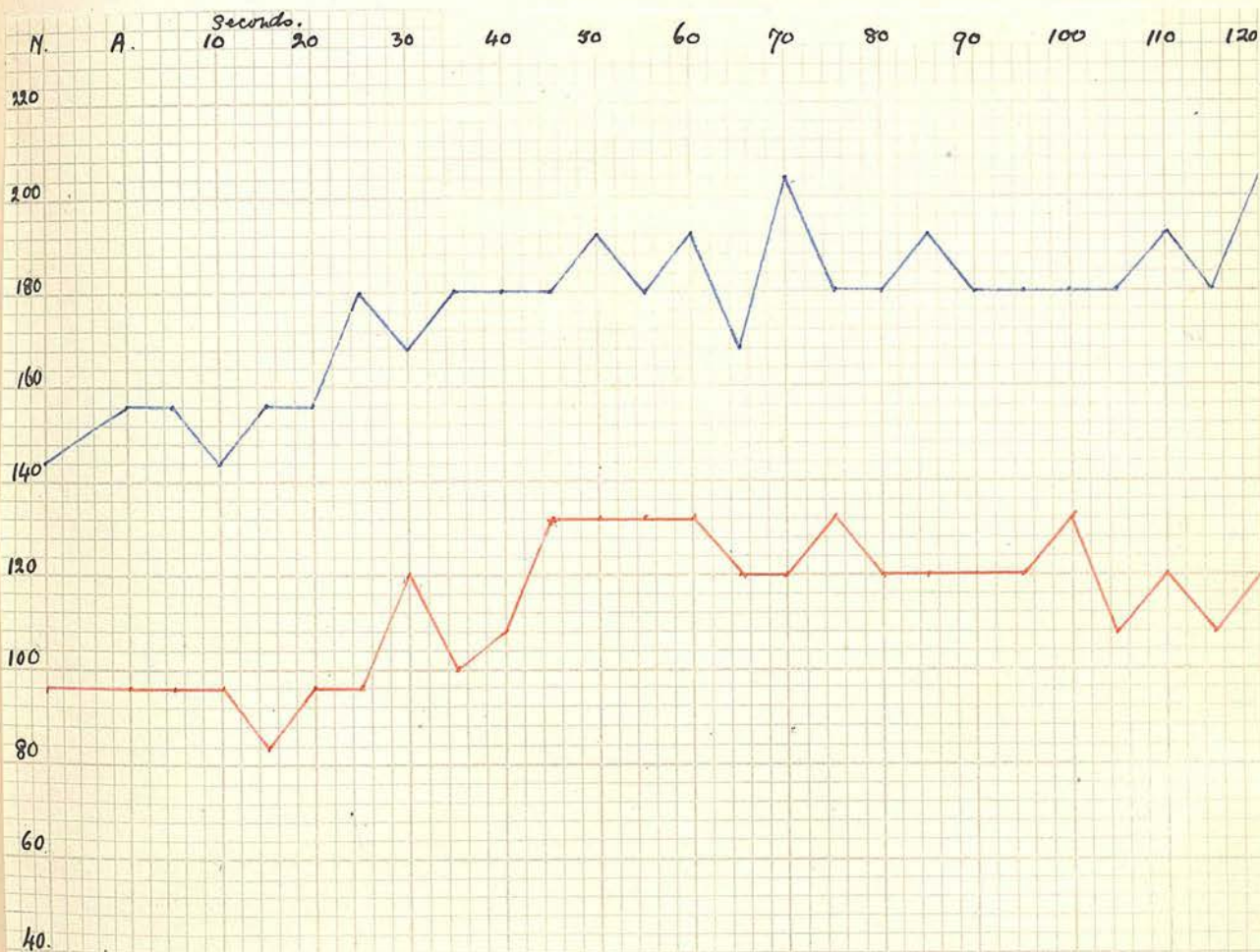
Atropin Release.

Def. Digit - black
after Digit - red.

N - before needle

A - Atropin injected.

NO RELEASE.



40.
Pulse
rate.

Name A.W. T. Digil. 20 cc.

age. 39. Atropin Release.

23.2.27.

Paroxysmal Fibrillation.

Bef. Digil - black.
after Digil - red.

N - before needle

A - Atropin injected.

A GENERAL ANALYSIS of all the CASES

GAVE THE FOLLOWING

RESULTS:-

NORMAL HEARTS.

Case No.	Name	Sex	Before Digit.			After Digit.			Digitalis.		
			Bef. A.	After A.	T.	Bef. A.	After A.	T.	Brnd.	Rate.	Dose per lb.
22.	B---s	M	108	120.	+	108	132	±	W	0.1.	15.9cc
23	G---d	M	120	165.	+	156	204	+	W	0.1	13.7cc
24	W---y	F	132	144	+	132	144	+	W	0.1	11.3cc
25	T---e	F	96	144	+	84	132	-	H	0.125	13.0cc
26	S---d	M	84	132	+	84	144	±	H	0.125	13.7cc.

Auricular Fibrillation Cases.

I. Showing complete Vagal Release.

Case.		Name.		Sex.		Before Digit.		After Digit		Digitalis	
No.						Bef.	After	T	Brnd.	Rate	Dose.
						A.	A.	A.	A	per lb.	
3.	K---	y.	F.			144	168	+120	168.	+	W 0.1. 10.2cc
4.	L---	p.	M.			132	192.	+108	192	+	W 0.1 15.6cc
5.	P---	r.	M.			108	132.	+75	135	+	W 0.1 13..6cc
6.	R---	e.	M.			72	156.	+96	156	-	H. 0.1 13.6 cc
15	S---	e.	M.			108	192.	-96	180	-	H. 0.125 12.0cc
20	B---	n	M.			144	180.	+84	180	+	H. 0.15 15.0cc

Auricular Fibrillation Cases.

II. Showing INCOMPLETE Release.

Case. Name. Sex. Before Digit. After Digit. Digitalis.											
No.			Bef. A.	After A.	T.	Bef. A.	After A.	T.	Brnd	Rate per lb.	Dose.
2.	C---c	M	120	144	+	84	120	+	H	0.1	14.5cc
8.	R---s	F	132	168	+	96	120	-	W	0.1	11.0cc.
9.	S---w	F	144	204	-2	108	180	-5	H	0.1	18.2cc.
10.	T---n	M	144	216	+	90	135	+	W	0.1	11.2cc
12.	W---s	F	96	168	+	72	144	-	H	0.1	17.3cc
* 13.	S---c	F	108	144	-2	108	120	-2	H	0.1	13.0cc
o 14.	M---d	F	108	168	+	96	120	+	H	0.1	11.3cc
16.	B---y	M	132	168	-3	72	120	-3	H	0.125	18.5cc
17.	M---y	F	108	192	+	84	168	+	H	0.125	12.7cc.
18.	B---l	M	120	216	-	108	168	-	H	0.1	15.3cc
x 19.	C---l	M	120	168	+	84	108	+	H	0.15	22.7cc
↑ 21.	C---d	F	168	204	+	196	120	+	H	0.15	36.5cc

↑ Vomited 4 times after Digitalis.

x All Atropin not in vein.

* Under Digitalis for 2 months prior to dose.

(Over)

o Delay occurred in injection of Atropin before Digitalis
as the vein was occluded by band till one minute after.

Auricular Fibrillation Cases.

III Showing no Vagal Release.

Case.		Sex.	Before Digit.			After Digit.			Digitalis.		
No.			Bef. A.	After A.	T.	Bef. A.	After A.	T.	Brnd.	Rate per lb.	Dose.
1.	B---y	M	156	180	-5	144	156	-3	W	0.1	13.2cc
*7.	R---s	F	144	168	-2	144	156	-2	W	0.1	17.7cc
11.	W---e	M	180	204	-1	156	168	-1	W	0.1	16.8cc

* Died 14 days later.

Cases 11 and 11. suffered from severe myocardial damage.

Auricular Fibrillation Cases

after continuous Digitalis Therapy.

Case No. Name. Sex. Bef. A. T. After A. T. Dose of Dig. per diem. Duration of Dig. Dosage

28.	S---s	F	120.	180.	-	36 m.	12 mths.
29.	B---w.	F	156.	192.	-	45 m.	7 mths.
30.	C---m	M.	84.	- 108	-	21 m	2 $\frac{1}{2}$ yrs.
31.	B---n.	M.	84	- 168.	-	45 m	2 months.

RESULTS OBTAINED:-

1. Cases of normal Rhythm.

(1) Massive Digitalis dosage is shown to have no slowing effect upon the Cardiac speed, under conditions of normal rhythm.

(2) The degree of Atropin release obtained before and after massive Digitalisation is for all material purposes identical.

II Cases of Auricular Fibrillation.

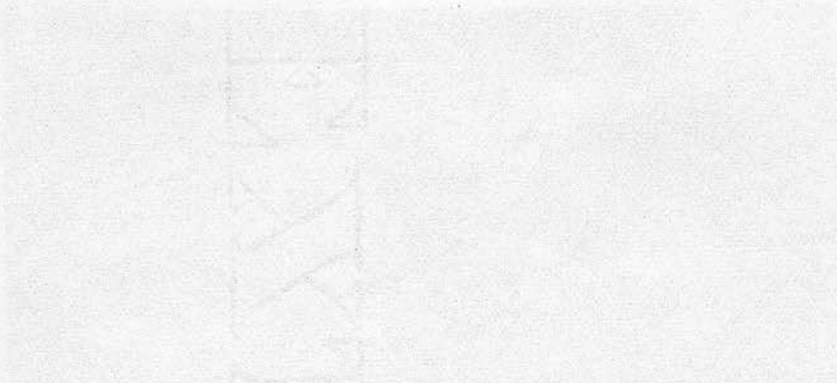
(1) Of the 21 cases of Auricular Fibrillation studied complete return to pre-digitalis release was obtained in 6 cases. i.e. 30%

(2) Incomplete return to pre-digitalis release was obtained in 12 cases - 60%. In two of these a minor breakdown in technique is believed to have occurred. In two others there is reason to believe that digitalis administration had reached a toxic stage.

In all these cases however, a definite release was obtained, the average rise after Atropin administration under Digitalis was 44 beats, but the average difference between pre-digitalis, and post-digitalis release was 45 beats. The evidence that the degree of release is proportionate to the actual dose of Digitalis is suggestive, but very far from clear.

(3). Three cases in the series gave no release either before or after Atropin. There is some reason to believe that all three had myocardial damage.

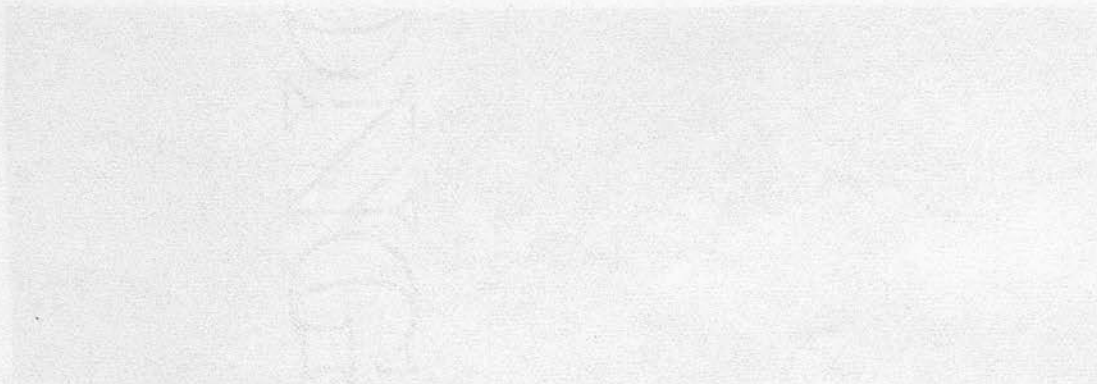
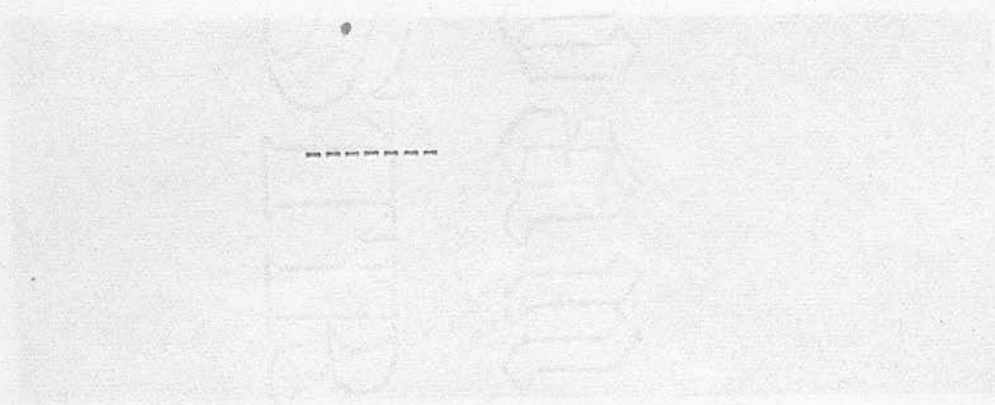
(4), Atropin release was obtained in 4 cases after prolonged use of Digitalis. In all cases a moderate release was found with an average of 50 beats. but no knowledge of the degree of release before Digitalis administration was available, except in case 31, of which see chart.



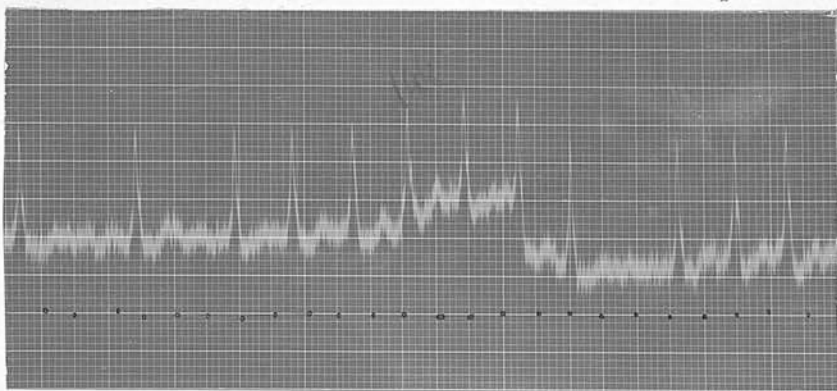
EXAMPLES SHOWING TYPICAL TRACINGS

and

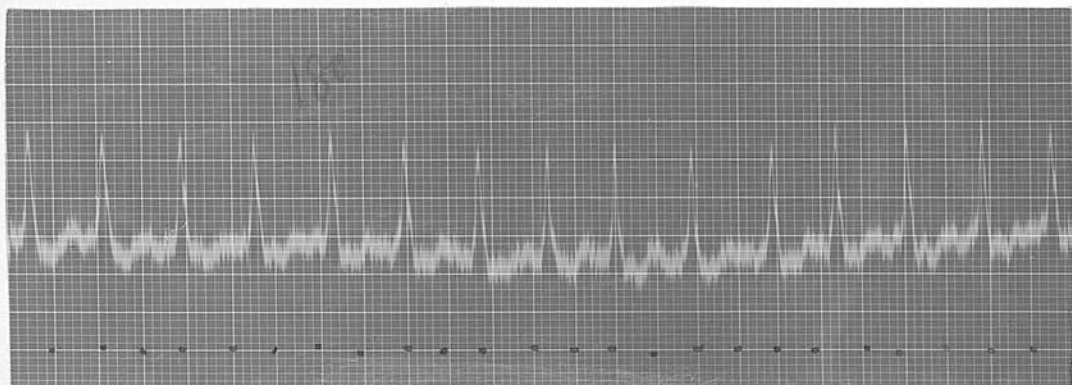
METHOD of ENUMERATION.



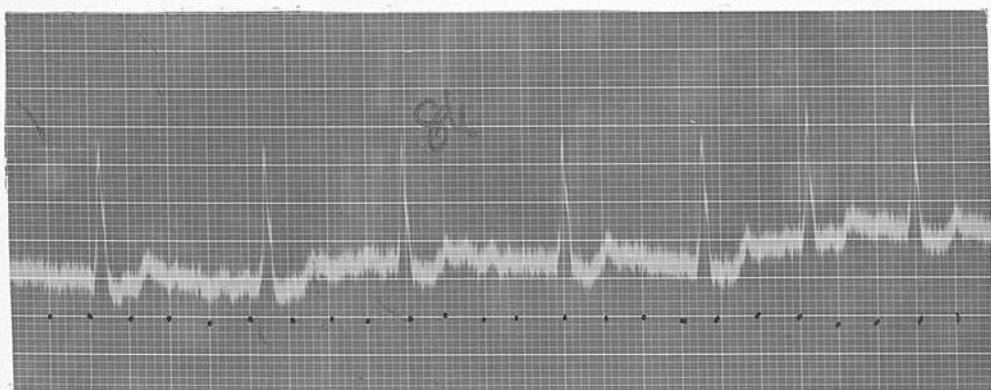
BEFORE DIGITALIS-Before Atropin - Rate 144 Wm. Brown
per min. Age 41.



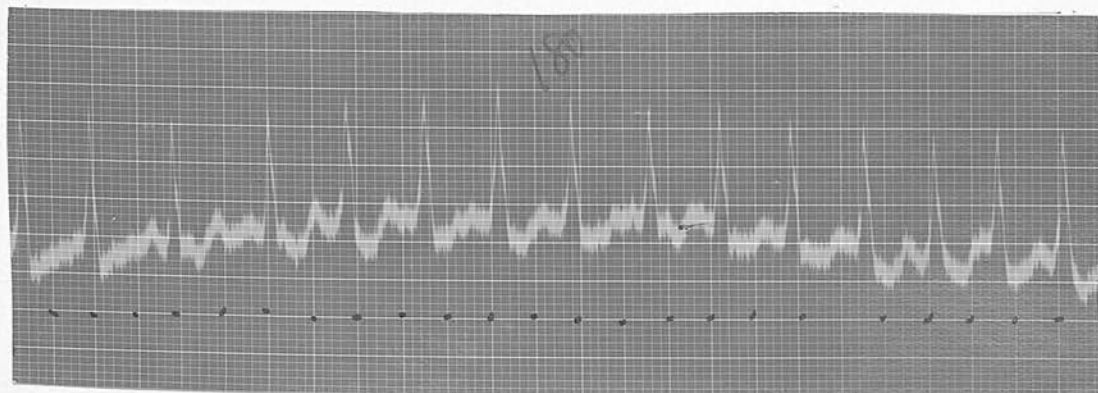
After Atropin - Rate 180 per min.



AFTER DIGITALIS - Before Atropin - Rate 84 per min.



After Atropin - Rate 180 per min.



BEFORE DIGITALIS

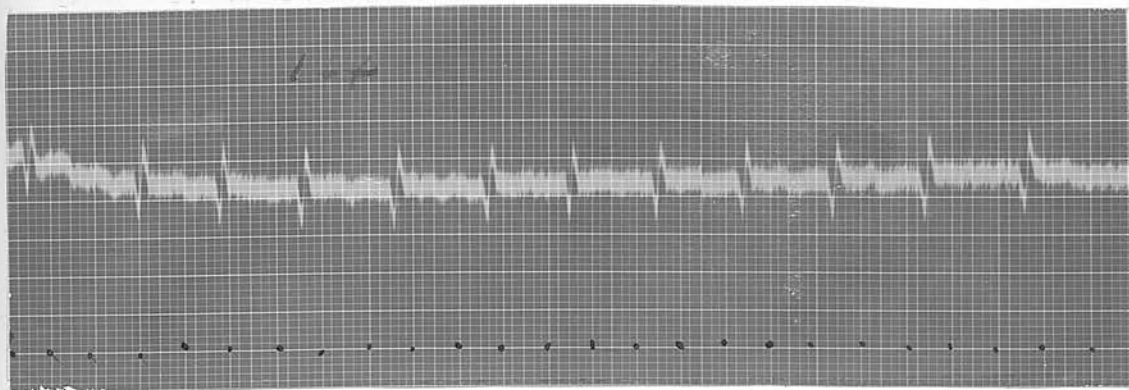
-

Before Atropin

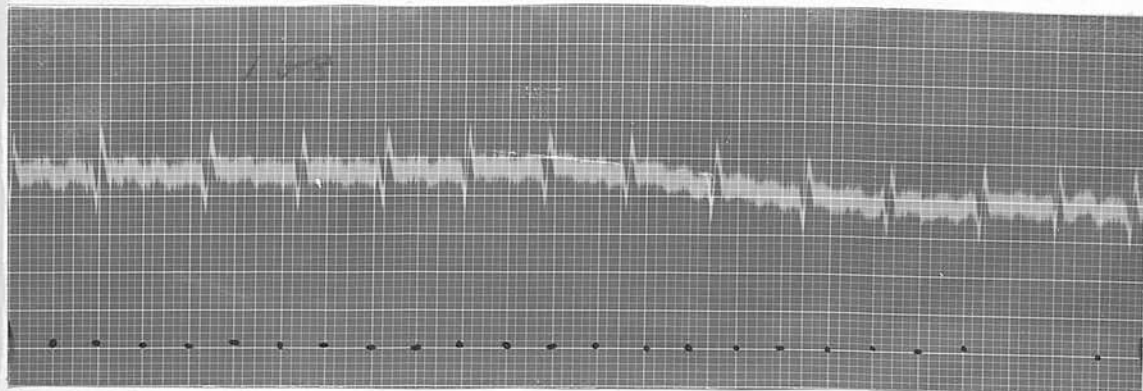
-

Rate 144
per min.

Agnes Kelly
Age 33.



After Atropin - Rate 168 per min.



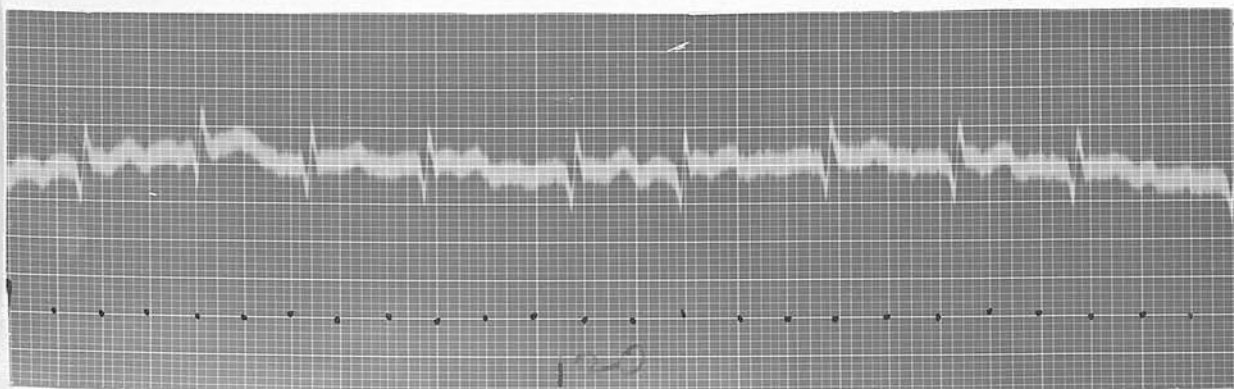
AFTER DIGITALIS

-

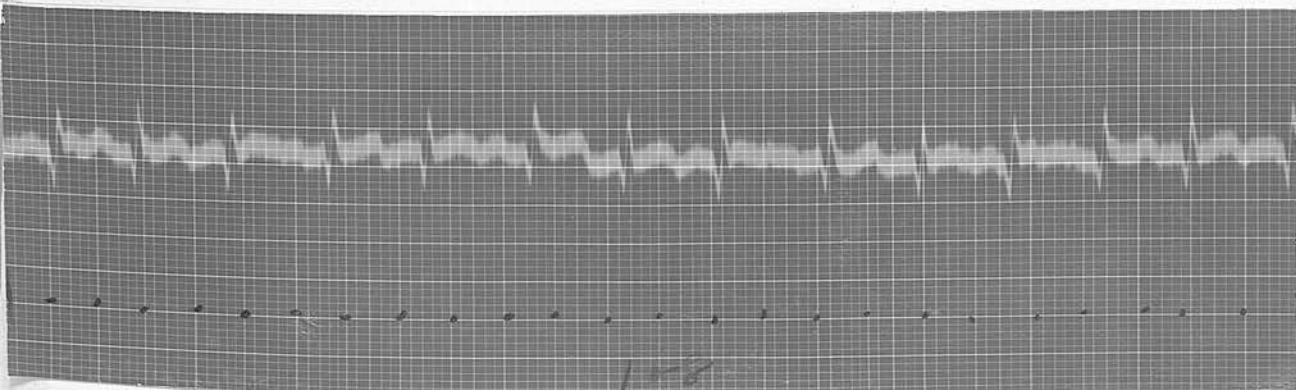
Before Atropin

-

Rate 120 per min.

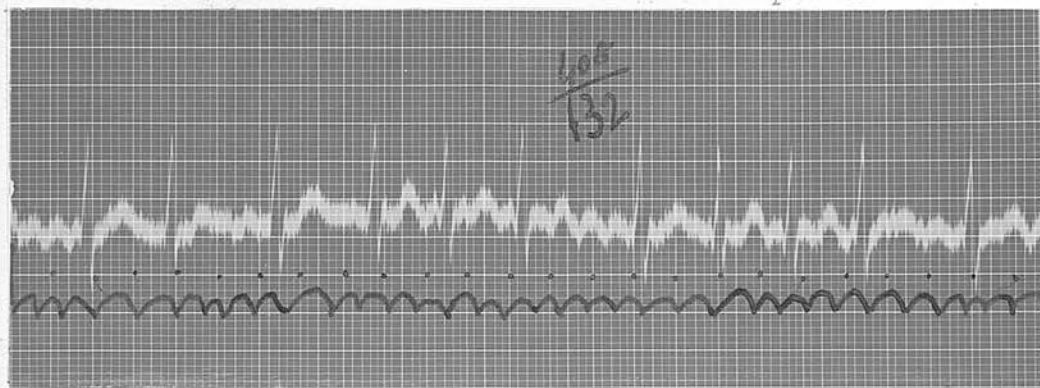


After Atropin - Rate 168 per min.

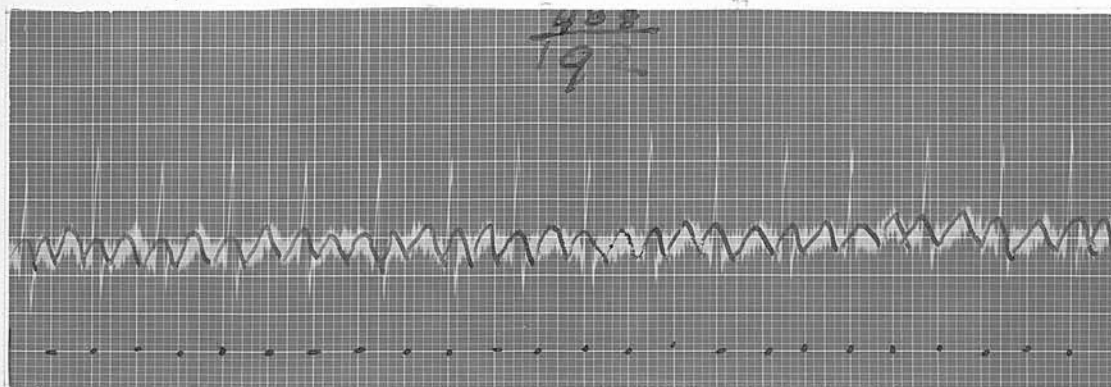


BEFORE DIGITALIS - Before Atropin - Rate 132
per min.

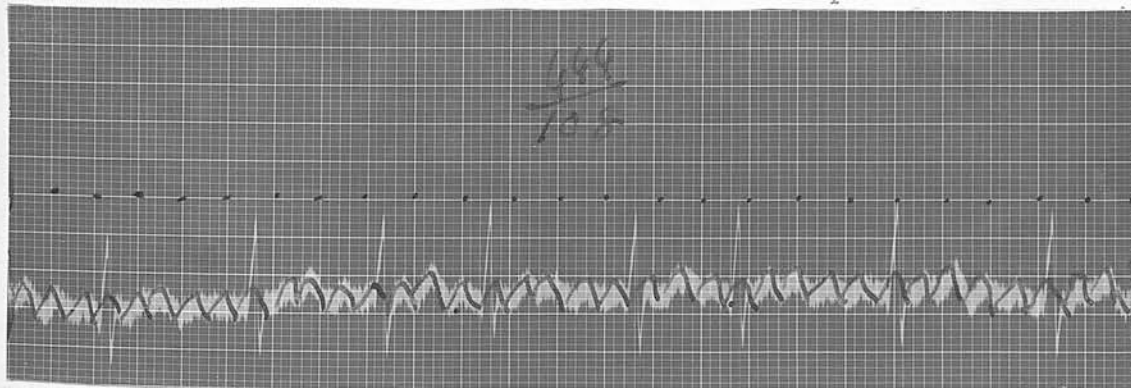
John Lindrop
Age 40



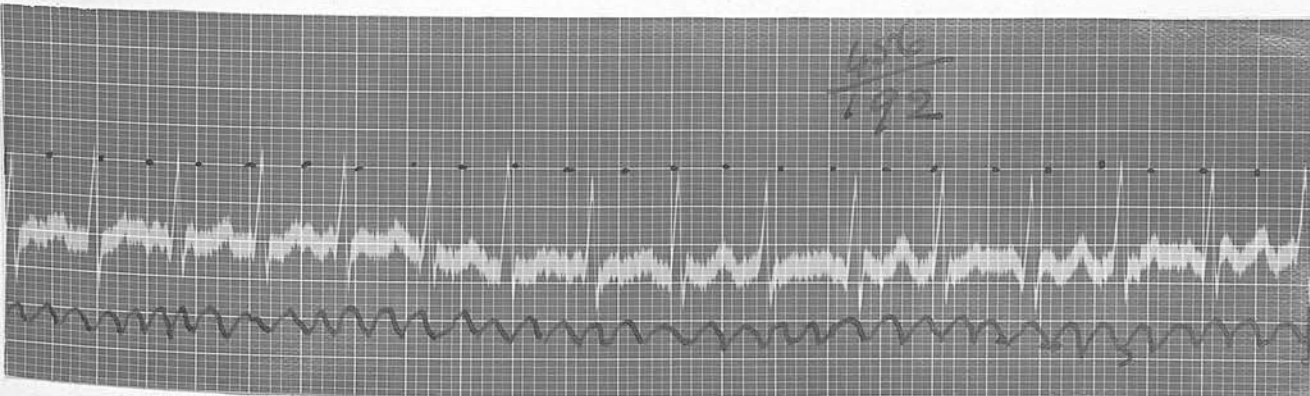
After Atropin - Rate 192 per min.



AFTER DIGITALIS - Before Atropin - Rate 108
per min.

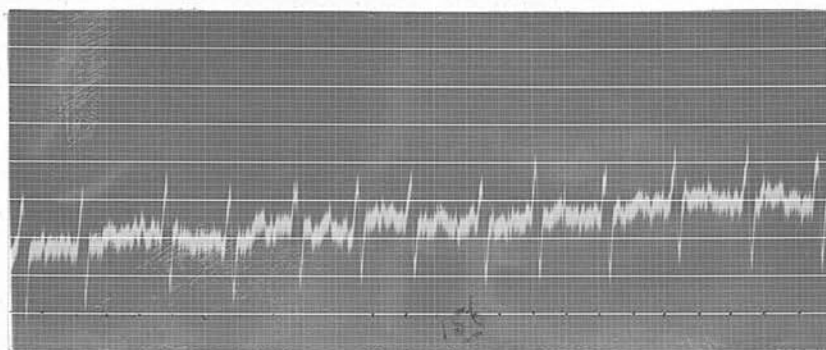


After Atropin - Rate 192 per min.

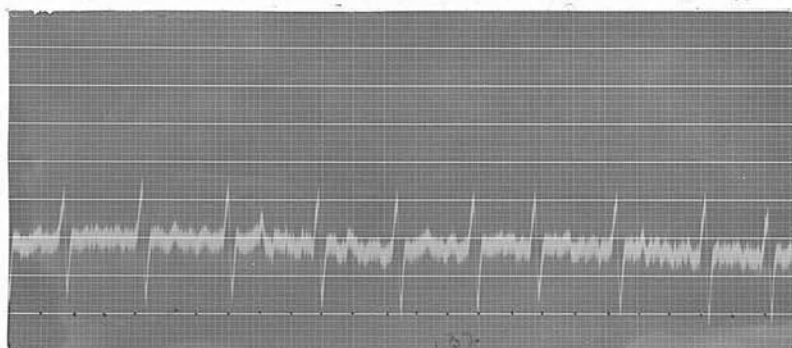


TRACINGS SHOWING FULL DIGITALIS EFFECT WITHIN 8 HOURS

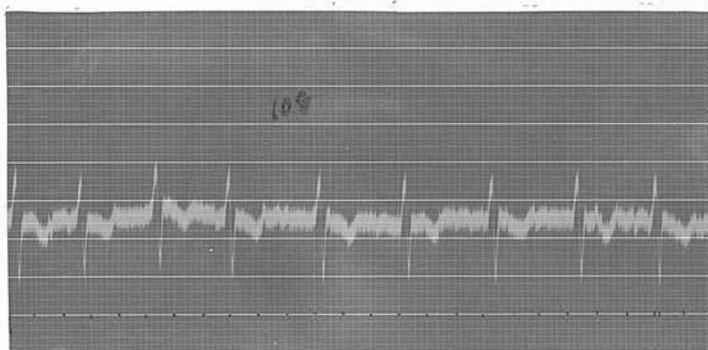
Before Digitalis T. Upright Vent. Rate 156



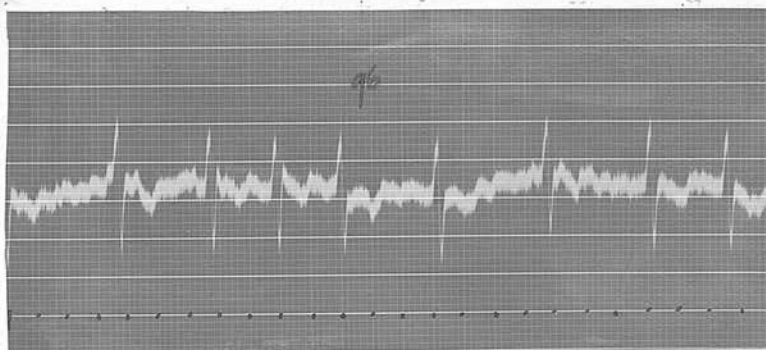
2 Hours After T. Digitalis - 20 ccs. T. Upright Vent. Rate 132



4 Hours After T. Invert. Vent. Rate 108.



8 Hours After T. Invert. Vent. Rate 96.



DISCUSSION OF RESULTS.

The effect of Atropin.

In the experiments carried out, the dose of Atropin was in all cases 1/25 gr. Atropin Sulphate given intravenously.

The maximum release occurred :-

- (a) Before Digitalis, on an average 46 seconds after completed Atropin injection,
- (b) After Digitalis - on an average 49 seconds after injection.

The earliest release obtained was 15 seconds after the injection, and the latest was 60 seconds.

The average moment of release before Digitalis was 31 seconds after the injection of Atropin, and 33 seconds after the administration of Digitalis.

There was no release whatever in three cases, of these one died 14 days later, and from electrocardiographic evidence, we had reason to suppose that the other two patients suffered from severe Myocardial damage.

The results of the experiments in these cases would support the theory of Cushny, that Digitalis acts on the myocardium.

In the cases where there was only a partial release it must be taken into account that some of the female patients were obese, and that there was the possibility of the drug not entering in its entirety into the vein.

This was known to have happened in one male patient. In another ~~xxx~~ patient delay occurred in the injection of Atropin before Digitalis as the vein was occluded by the constricting band, till one minute after the injection.

The effect on the Auricular speed in the cases counted was variable.

LEWIS (XIV) states that the effects of Atropin are naturally the reverse of Vagal stimulation, since the drug abolishes vagal tone.

In experiment, Atropin tends to increase the transmission intervals, and to prolong the refractory period of the rapidly beating Auricle. Atropin should therefore, slow the Auricular rate, when the Auricles are fibrillating, this effect is actually witnessed, both in experiment and clinically, the effects are slight but definitely recognisable. The drug has a similar slowing action in flutter, though it is again slight."

In the one case of flutter that was investigated in our experiments slight slowing was observed.

Attached, but not included in the records analysed is a table of results found in the analysis of Auricular rates.

It must first be stated that no special leading from the chest ~~wald~~ was used as would have been more effectual, owing to the necessity of showing the T wave in Lead II.

There was an increase in Auricular speed before and after Atropin in 10 cases, and a decrease in speed in four. The difference in all was slight.

The effect of Digitalis was to increase the speed in three cases, and to decrease it in two cases, (see chart.)

AURICULAR SPEEDS.

Case No.	<u>Before Digitalis.</u>			<u>After Digitalis.</u>		
	<u>Begin.</u>	<u>Middle.</u>	<u>end.</u>	<u>Begin</u>	<u>Middle.</u>	<u>End.</u>
17.	A. $\frac{360}{108}$ V. $\frac{360}{108}$	$\frac{396}{192}$	$\frac{324}{168}$	$\frac{348}{96}$	$\frac{372}{168}$	$\frac{360}{156}$
29	-	-	-	$\frac{408}{156}$	$\frac{324}{192}$	$\frac{336}{168}$
15	$\frac{516}{108}$	$\frac{372}{192}$	$\frac{408}{168}$	$\frac{528}{96}$	$\frac{372}{180}$	$\frac{480}{156}$
20.	$\frac{396}{156}$	$\frac{336}{180}$	$\frac{372}{168}$	$\frac{328}{84}$	$\frac{384}{180}$	$\frac{384}{156}$
4.	$\frac{384}{156}$	$\frac{408}{192}$	$\frac{396}{198}$	$\frac{444}{108}$	$\frac{456}{192}$	$\frac{444}{168}$
6	$\frac{300}{60}$	$\frac{372}{156}$	$\frac{132}{420}$	$\frac{384}{72}$	$\frac{396}{156}$	$\frac{384}{132}$
21.	$\frac{348}{180}$	$\frac{372}{204}$	$\frac{346}{192}$	Not Countable.		
3	Not Countable.			$\frac{396}{120}$	$\frac{444}{168}$	
5	$\frac{372}{108}$	$\frac{108}{108}$	$\frac{396}{132}$	Not Countable.		
* 27.	$\frac{324}{168}$	$\frac{300}{204}$	$\frac{300}{192}$	$\frac{312}{72}$	$\frac{312}{144}$	$\frac{312}{108}$

The top figures in each series - Auricular rates.
The bottom " " " " " Ventricular "

* Case of flutter.

EFFECT ON VENTRICULAR SPEED.

The effect on the Ventricular speed before and after Digitalis is seen in the tables analysing the results of the experiments.

Effect upon the form of Electrocardiogram.

There was no change noted in the form of the (a) undulations, or, (b) of the Ventricular complexes. As regards abnormal beats a table is attached, showing an analysis of the abnormal beats found and their frequency.

Out of a total of 30 cases, 12 patients show extra systoles. There is only one case of coupling which lasted for 30 seconds. One patient showed frequent extra systoles before and after Digitalis, one showed no abnormal beats in spite of showing toxic Digitalis effects. All the others showed a negligible frequency of abnormal beats (See Chart.)

ABNORMAL BEATS.

Case No.	Before Digitalis.		After Digitalis	
	Before	After	Before	After
	Atrop.	Atrop.	Atrop.	Atrop.
20	-	-	1	3
19	7	-	-	4
30	-	-	-	Coupled for 35 seconds at highest spd.
21.	After toxic dose of Digitalis no abnormal beats.			
4	-	-	-	1
7	-	1	-	2
9	-	1	-	-
13	-	2	-	-
10	Frequent extra systoles		Frequent extra Systoles	
12	-	1	-	-
11.	-	-	5 extra systoles present with variation in Q.R.S. form.	
2.	Frequent Extra systoles from several ventricular points		Extra systoles uncommon.	

CONCLUSIONS:-

Atropin by the intravenous route in the dose used can be given with safety. It induces but slight constitutional disturbance, e.g. vertigo, dry mouth, dilated pupils, and slight mental excitement, all transitory and not serious.

Vagal release can be obtained in 30 seconds from the moment of termination of the injection of the Atropin. It can be expected with certainty, and is therefore easily recognised, and can be recorded graphically. It provides a highly satisfactory method of applying the test.

Larger doses are not regarded as justified until the present dose has been applied clinically and found free from objection. Further work on the subject may cause a change of opinion.

EFFECT of DIGITALIS.

The effect of Digitalis, given by the massive method in one draught, gives the following results:-

- (1). The full therapeutic effect can be obtained in from 6-8 hours. (Pardee XVI).
- (2) The effect is to some extent dependent on the potency of the tincture.
- (3) At present there is no satisfactory Pharmacological standard, and experiments with different tinctures are not strictly comparable.

In the foregoing, experiments two Brands of the tincture were used, and were supplied by two Manchester firms of repute. That marked "W" in the charts was a roughly standardised tincture by the frog method.

That marked "H" was guaranteed as 100% Tincture after assay in the Pharmaceutical Societies Laboratories, London, and appeared to be the more potent.

- (4). At the rate of 0.1cc per lb. body weight, a really full Therapeutic effect was not obtained with either tincture, in that the T wave in Electrocardiogram in Lead II was not always inverted, and coupling and vomiting did not always occur.
- (5) At the rate of 0.15 cc per lb. the dose was found to be too high, and vomiting resulted.
- (6) The probable correct dose is 0.125 cc. which would indicate a tincture of less strength than that used by Eggleston, and standardised by the Hatcher and Brodie cat unit method.

- (7) The toxic effects of Digitalis, at the correct dose, and with due regard to the potency of the preparation do not occur.
- (8) The clinical benefit to the patients is rapid and remarkable. From being in a state of acute distress, they are made comfortable in a few hours, with a pulse rate for example, reduced from 144 -84.
- (9) The effect on the Auricular Undulations was variable, as regards (a) speed, as has already been pointed out~~out~~, and ^{as} regards (b) size there was no definite change noted.
- (10) The effect on the ventricular response with reference to:-
 - (a) speed has already been discussed in an analysis of the experiments done.
 - (b) form. There was no change found in the form of the ventricular response, before and after the administration of Digitalis.
 - (c) Ectopic beats. The occurrence of these was infrequent, and has already been discussed.

Prima Facie the effect of Digitalis is not demonstrable either on (a) the Auricle in fibrillation, or on (b) the Ventricle except in so far as the speed of the latter is concerned.

It must be supposed therefore that it acts on the functional tissue.

The question at issue is whether the primary effect is upon the junctional tissue in the heart, or on the Cardio-Inhibitory centre in the Medulla. Section of the Vagus gives the answer as seen in animal experiments already quoted, and the same effect is accomplished clinically, by adequate Atropin administration.

If Digitalis acts on the Medullary centre and Atropin acts upon the Vagal endings in the heart, then full atropin effect must effectually block the vagal stimuli. "No amount of shouting will be audible in the telephone, if the receiver is disconnected" (IV.footnote p.105.), but the receiver must be completely disconnected - half contact might produce an audible shout and inaudible whisper. Therefore it is still tenable that when Digitalis is given to a toxic effect, Atropin must be similarly used, to ensure complete release. To enlarge the amount of Digitalis in massive dosage is safe because vomiting terminates absorption; to enlarge the Atropin dose to correspond is regarded as unsafe and unjustifiable at the present stage of this work. Absence of release in toxic Digitalis effects must for the time therefore, be discontinued.^{unred.}

Excluding these cases:-

- (1) Complete release shows there is undoubted Digitalis effect via the Vagus.
- (2) Partial release - the amount by which they fall short of complete release is often small.

Recording the pulse rate at 5 second intervals gives a multiplicand of 12, so that the variation in the

1. The count may be 24 owing to unequal spacing and fortuitous arrangement of beats at the beginning, and end of the time period.

(3) No release may occur in 3 groups.

(1) None before, and none after Digitalis.

(2) Release before and none after.

(3) No release before, and release after.

The meaning of this is at present obscure.

Intravenous injection of a small amount of fluid, average 10 minims is not an absolutely certain procedure in women, and in obesity generally it is very difficult to be certain that the drug is in the vein.

Possibly the best proof is adequate therapeutic result i.e. release. Absence of any release is probably proof that the drug did not enter the vein.

(4) Release after prolonged Digitalis and in the presence of signs of full therapeutic dosage shows a vagal effect.

(5) Digitalis action in Fibrillation is a thing apart having no counterpart when the heart is in normal rhythm. In the normal cases there was - no Digitalis slowing. The release was identical.

CONCLUSIONS.

1. Literature holds much evidence that in animal experiments, either vagal section or Atropin release, gives complete release of the digitalised heart.
 2. That some records of clinical experiments also show complete, or nearly complete, release.
 3. That records published are all open to the double objection of :-
 - (a) The length of time allowed to elapse between pre-digitalis, and post-digitalis release.
 - (b) Inadequate Atropin dosage by a route with no fixed time reaction.
 4. That the technique adopted in this series is free from these objections, and that further, the test has been made on undoubted therapeutic effects, as opposed to obvious toxic effects.
 5. That 30% of cases demonstrate the whole Digitalis effect to be Vagal, and that 60% ^{more} ~~and~~ show that the effect is largely Vagal.
 6. It is believed. that if and when, a larger Atropin dose can be safely given intravenously, the whole effect of Digitalis will be found to fall upon the Vagus, whether the drug has been given in a single or massive dose, or has been continued in small doses over many months.
-

Since this work was completed, the following case of Auricular Fibrillation was released with Atropin:-

Digitalis (H) at the rate of 0.15 cc.per lb body weight was given. i.e. CC XXI, and at the second half of the experiment 1/25 gr.Atropin was injected, and one minute later a further 1/50 gr.Atropin was put into the vein, to see if any greater release could be obtained.

Towards the end of the expirment 1/18 gr. of Pilocarpine Nitrate was injected intravenously, in order to see if it had any antidotal effect to the Atropin.

In analysing the result of the experiment it was found that the first injection of Atropin i.e.1/25 gr. had produced a complete release, and that the additional 1/50 grain, did not produce any further release. The Pilocarpine did not cause any appreciable slowing, beyond what usually occurs at the end of 2-3 minutes experiment.

As a result of the experiment the patient was considerably upset, and suffered from a fair degree of cerebral irritation. In view of these facts it is manifestly not altogether safe to administer larger doses of Atropin than 1/25 gr. until some work has been done to show that Pilocarpine can be safely and efficiently used as an antidote..

Case No,	Dose of Dig.	Before Digitalis		
		Before A.	After A.	T.
33	0.15 cc.per lb. cc.XXI	84	120.	+
T.	After Digitalis			
	before A.	after 1/25 gr.A.	after 1/50grA.	after Pilo.
-	72	120	120	lowest 96

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